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GAUCHER'S DISEASE.

A REPORT OF TWO CASES IN INFANTS.

By J. H. Mason Knox, Jr., Ph. D., M. D., H. Roswell Wahl, M. D., and Harry C. Schmeisser, M. D., Ph. D.

(From the Thomas Wilson Sanitarium, the Department of Pathology of the Western Reserve University Medical School, and the Departments of Pediatrics and Pathology of the Johns Hopkins University.)

The cases of Gaucher's disease reported in the following paper occurred in two children of the same parents that came under observation during a period of two years. The first child was admitted to the Thomas Wilson Sanitarium in the service of Dr. Knox. The disease ran a fatal course in a comparatively short time, the clinical and anatomical findings, the latter studied by Dr. Wahl, being prepared for publication in January, 1915. About one year before, the second child had been admitted to the Harriet Lane Home of the Johns Hopkins Hospital in the service of Dr. Howland. In this case also the clinical aspects were studied by Dr. Knox and an excised gland was examined by Dr. Wahl. The case likewise ran a rapidly fatal course and was studied anatomically by Dr. Schmeisser. It was decided to include the two cases in one report.

Historical.—Through the recent investigations, notably those of Bovaird, Brill, Mandelbaum, Libman, Reuben and others, the uncertainty surrounding the disease described by Gaucher in 1882 has been largely removed. It is now agreed that the term "Gaucher's disease" can be properly applied to only a small group of splenomegalies, namely, to those cases in which the organs show the presence of certain distinctive large cells. Of the total of 16 cases reported since 1882, 12 have been described in the last decade and three, exclusive of our cases, within two years. Unquestionably the condition is more prevalent than has been suspected, and as the peculiar features of the disease become more generally known, the number of cases reported will probably increase rapidly.

The literature of the subject has been so thoroughly presented by Mandelbaum that a further review is unnecessary. It may be helpful, however, to present briefly in tabular form the instances of Gaucher's disease—proven to be such by microscopic examination—heretofore reported and to comment briefly upon the more important features. The cases accepted by Mandelbaum, together with two more recent ones, are summarized in the accompanying table (see pages 4 and 5), an analysis of which gives the following more important data:

Analysis of Table: *Sex.*—The disease appears to be more prevalent in the female. Of the 16 patients there were but three males.

Age.—It may manifest itself at any age, but the majority of cases reported have been in young adults. The oldest patient, Marchand's,[5] was a woman 44 years old; the youngest, Niemann's,[14] was a child of 14 months. It is probable that the condition in the older patients had existed for years before being recognized.

Symptoms.—The onset of the disease is insidious, the symptoms being vague and indefinite. A feeling of weight accompanying the enlargement of the abdomen was usually present.

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Eleven of the patients had some form of hemorrhage, usually epistaxis or bleeding from the gums or into the skin. Dull abdominal pain was complained of in 10 instances. Œdema of the feet was noted in four cases; in four there was fever and in four a moderate degree of dyspnœa. Three of the patients suffered from excessive sweating, and in several there was more or less indigestion. In all there was gradual loss of weight. Death ensued from exhaustion or from some intercurrent malady.

Physical Signs.—The most constant physical sign was the enlargement of the abdomen, due primarily to the increase in bulk of the spleen and liver.

Spleen.—The spleen is described as "filling the abdomen" in a number of instances. In Case 9 it reached a maximal size —45 x 25 x 13 cm.—and weighed 8100 gm. The relation of the spleen to the body weight, which is normally about 1 : 400, may in this condition be altered to 1 : 5 or 6. In each instance the organ retained its normal outline and was firm and resilient to palpation.

Liver.—Enlargement of the liver was noted in 14 cases. It was not so marked as was that of the spleen, and seemed to occur at a somewhat later period. The organ was firm and its shape was not altered.

Lymph Glands.—The superficial lymph glands were moderately enlarged in 10 instances, and in three additional cases certain internal groups of lymph glands were enlarged. In two cases the glands were not enlarged.

Color of the Skin.—Gaucher described his patient as having a skin of a peculiar leaden hue, which became more pronounced towards the end of the illness. A similar yellowish or brownish discoloration, most marked on the face and extremities, was noted in 11 cases. In two "slight jaundice" was mentioned, and in three cases no pigmentation was described.

Conjunctival Thickening.—Brill and Mandelbaum have described a "brownish-yellow wedge-shaped thickening of the conjunctiva" extending from the cornea to the inner and outer canthus. They consider this of diagnostic significance. This alteration in the conjunctiva has not been noted in the majority of the cases thus far reported, but its importance for diagnosis must be determined later.

Blood.—The blood presents the picture of a secondary anæmia of varying severity, dependent upon the course of the disease. In a few cases the red cells and the hæmoglobin are only slightly altered. The most striking feature of the blood picture is the reduction in the number of leucocytes. This appears to be a constant finding. The minimal white count reported was 500 to the cubic millimeter. The differential count is usually within normal limits, and abnormal cells have been found only rarely in the circulating blood.

Family History.—The incidence of the condition in other children of the same parents is to be particularly noted. In many of these additional cases Gaucher's disease was not proven by pathological examination, but presumptive evidence of the condition was present, *i. e.*, a large spleen and other important signs. The family history is recorded in 12 of the above cases, and in nine of these an enlarged spleen and symptoms strongly suggesting the disease were found in one or more brothers and sisters of the patient. This tendency to appear in several members of the same generation is apparently a suggestive feature of the malady. In no instance was the disease transmitted from parent to offspring.

Cause of Death.—Gaucher's disease is essentially chronic and may last for years. Niemann's case and those we are about to describe—all in infants—suggest that the process is more intense in early life. Of the seven patients treated expectantly, two died from exhaustion after much emaciation, and five from intercurrent affections or from accident.

Splenectomy.—The spleen was removed in nine cases. Three of these patients died shortly after the operation. Six were reported living at various periods after the operation, one after 41 days, one after six weeks, three after five weeks, and one after 16 months. In most of these the sense of weight in the abdomen had been relieved, but there is no evidence that the further progress of the disease was arrested.

Syphilis and Tuberculosis.—An effort was made to determine whether syphilis or tuberculosis was concerned in the etiology of the condition. Of the 16 cases no evidence of syphilis was found at autopsy in two instances; in five others the Wassermann test was negative; in only one (Niemann [4]) was it positive. In 13 of the 16 cases no tuberculosis was found on examination of the organs or of the excised spleen. Tuberculous lesions were present at autopsy in three instances. It can be confidently assumed that neither syphilis nor tuberculosis plays an etiological rôle in this disease.

Microscopical Findings.—In each instance the presence of peculiar, pale round or oval cells, having an average diameter of from 20 to 40 microns and one or several relatively small nuclei, is the characteristic feature of the disease. In many of the cells the protoplasm stains poorly, is finely granular and vacuolated. Their relative number varies greatly, depending apparently upon the severity of the process. In some instances they occupy almost the entire organ; or they may be found singly or in groups among the normal cells. The spleen, liver and lymph glands are most frequently involved, although the bone-marrow and, as in our cases, nearly all the tissues of the body may be affected.

Origin of the Cells.—The origin of these cells has been much discussed and will be referred to in detail later on in the paper. The views thus far held are that they arise either from the reticulum or from cells lining the blood and lymph vessels.

Pathogenesis.—The cause of this remarkable condition is as yet unknown. It has no connection with a neoplastic growth, as Gaucher at first thought. No evidence of a bacterial or protozoan infection has been found. A number of writers have considered the disease dependent upon a chronic intoxication of an undetermined nature.

Case I.—S. G., a white female infant, 9 months of age, was admitted to the Thomas Wilson Sanitarium June 12, 1912.

***Family History.*—The father, a moderate user of alcohol, was 41 years of age and well. The mother was 38 years of age and**

well. Both parents were Russian Hebrews of small means. They had had 11 children, as follows:

1. A girl, 20 years, well.
2. A boy, died at 8 months, cause unknown.
3. A boy, 18 years, well.
4. A boy, died at 14 years of hip disease.
5. A girl, 14 years, well.
6. A girl, died at 1 year, "smothered in bed."
7. A boy, 11 years, well.
8. A girl, died at 18 months of convulsions.
9. A boy, 6 years, well.
10. A girl, 4 years, well.
11. A girl, the patient.

Past History and Present Illness.—The patient's birth was spontaneous. She was breast-fed for one month and then given a cow's milk mixture. She never thrived. For a month or two she vomited frequently, but for three months the milk was well retained. She slept well; cut two teeth at six months and was never acutely sick. The gain in weight, however, was very slow. The stools were from two to four in 24 hours, yellow and formed.

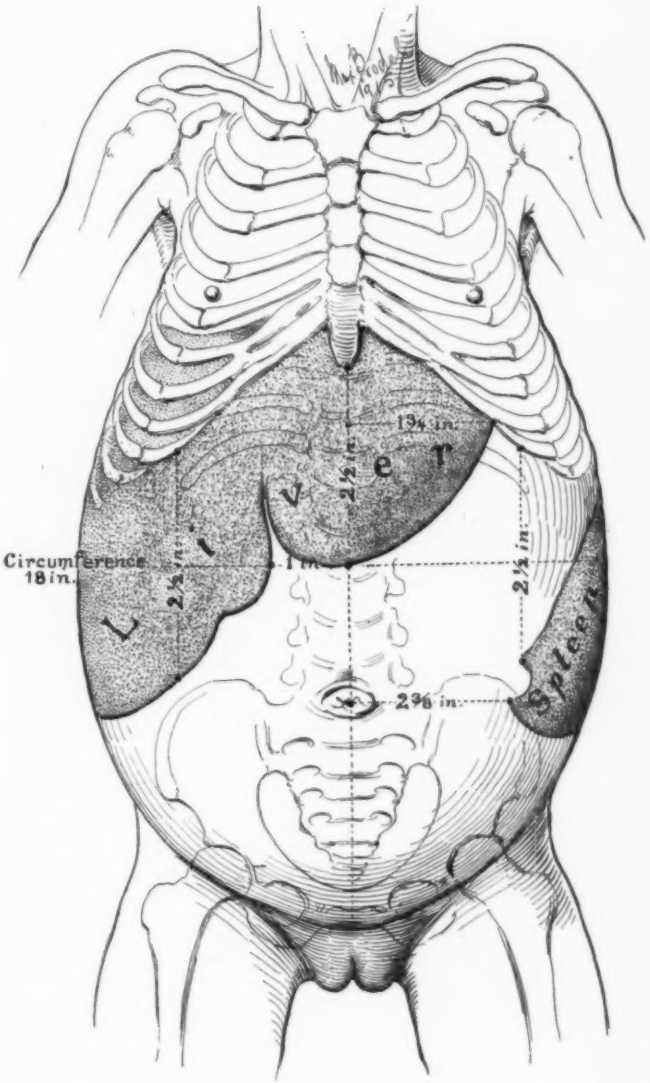
Physical Examination.—On admission the patient weighed 11 pounds. She was considerably emaciated. The skin was pale, with a slight brownish pigmentation, more marked on the face and arms. The abdomen was prominent; the cervical and axillary glands were slightly enlarged. The lungs were clear. The heart was not enlarged. There was a soft systolic murmur heard at the apex. The upper border of the liver began at the 6th rib and extended 2½ inches below the costal margin in the right nipple line. The surface of the liver was smooth and firm and the notch was readily palpable. The spleen was represented by a large mass extending 4½ inches below the left costal margin to the level of the umbilicus. The surface was firm and a little rough; the notch was palpable. The kidneys were not felt. The reflexes at the knee were present.

The blood examination on admission was as follows: Leucocytes, 10,400; red cells, 5,200,000; hæmoglobin, 90%. Differential count: Polymorphonuclears, 42%; large mononuclears, 5%; small mononuclears, 41%. Examination of the stools showed an excess of fatty acid crystals but no bile. During the first month after admission the child gradually lost in weight. On July 12, 1915, the blood condition was as follows: Red cells, 4,400,000; leucocytes, 25,400; hæmoglobin, 60%. Differential count: Polymorphonuclears, 59%; large mononuclears, 3.2%; small mononuclears, 36%; transitionals, 1%; myelocytes, 1%. The Wassermann and Von Pirquet tests were negative.

The patient continued to lose strength and weight. She was given a milk mixture successfully. There were from two to four fecal stools in 24 hours and no fever. There was a continuous loss of weight to 8½ pounds and death resulted from exhaustion at the age of 11 months, two months after admission to the sanitarium. The day before death a marked change took place in the differential count of the leucocytes. Their total number was increased to 35,000. The differential count was: Small lymphocytes, 82%; large lymphocytes, 9%; large mononuclears, 5%; polynuclears, 3%; unclassified, 1%.

AUTOPSY (four hours after death).—The body is that of a very emaciated white female infant 61 cm. long. The external ear contains a dried hemorrhagic discharge. The abdomen is very prominent. The veins are distended, but there is no caput Medusæ. The outlines of the lower edge of the liver and of the spleen are visible through the thin abdominal wall, the notches being easily recognized. The inguinal glands are considerably enlarged and are firm. The peritoneal cavity contains no excess of fluid. The liver extends 7 cm., the spleen 5.5 cm., below the costal margin. The heart weighs 25 gm., and shows no gross abnormalities. The lungs are voluminous, but everywhere contain air. In the lower right lobe the tissue feels denser and tougher than elsewhere and the pleura is a little more prominent. On section this part of the lung tissue is subdivided into small lobules by dense bands of fibrous tissue.

The *liver* is considerably enlarged and weighs 415 gm. It has a pale, grayish-pink color. Its surface is smooth and glistening and the capsule is not thickened. The lobules appear through the capsule as minute, pink dots surrounded by a pale yellow periphery. On section the organ cuts with a slightly increased



GAUCHER'S DISEASE—CASE I.—Diagram showing enlargement of liver and spleen. July 1, 1912.

resistance and shows a pale yellow or a slightly mottled grayish-yellow, moist surface, from which a thick yellowish mucoid material can be easily scraped off. This material does not feel greasy, but resembles condensed milk in consistence. There is a slight patchy fibrosis. The gall-bladder is small and contracted, containing about 1 cc. of thin yellow bile. The bile passages are patent. The common bile-duct is partly surrounded by three firm lemon-yellow lymph nodes, from 3 to 8 mm. in diameter.

No.	Author and Reference.	Sex.	Age at death.	Age at onset.	Chief Symptoms.	Physial Signs.			
						Spleen.	Liver.	Lymph glands.	Color skin.
1	Gaucher: Thèse de Paris, 1882.	F	30	7	Never robust; epistaxis, irregular menses, enlargement of abdomen. In last months, bleeding from gums, abdominal pain, œdema of feet, fever.	51 × 25 cm. (by palpation). Weight, 4700 gm.	Extends to umbilicus. Weight, 3500 gm.	Enlarged slightly.	Leaden
2	Collier: Tr. Path. Soc. London, 1895, XLVI, 148.	F	6	2	Never robust; enlargement of abdomen, epistaxis, emaciation, subnormal temperature.	Weight, 2070 gm.	.....	Not palpable, mesenteric glands large.	.....
3	Picou and Raymond: Arch. de méd. expér. et d'anat. path., 1896, VIII, 168.	F	32	4	Abdominal pain, from 4th year, menorrhagia, bleeding from gums, œdema of ankles, fever, loss of weight, enlargement of abdomen.	"Filled abdomen."	Three finger-breadths below costal margin.	Enlarged at hilus of spleen.	Slight
4	Bovaird: Am. Jour. Med. Sc., 1900, n. s., CXX, 377.	F	13	3	Increasing enlargement of abdomen, shortness of breath.	Weight, 6250 gm.	Not enlarged.	Enlarged slightly.	Brown
5	Brill, Mandelbaum and Libman: Proc. New York Path. Soc., 1904, IV, 143; Am. Jour. Med. Sc., 1905, n. s., CXXIX, 491.	M	30	14	Sweating, epistaxis, enlarged spleen, pain in splenic region and in legs, petechial hemorrhages, dyspnœa.	Weight, 5280 gm.	Weight, 4800 gm.	Enlarged in thorax and abdomen.	Brown
6	Schlagenhaufer: Virchows Arch. f. path. Anat., 1907, CLXXXVII, 125.	F	43	5	Enlargement of abdomen, œdema of feet, bleeding from gums, epistaxis, increasing weakness, pain over liver.	31 × 20 × 12 cm. Weight, 3510 gm.	Weight, 3000 gm.	Enlarged.	Brown
7	Von Herzel: Wien. klin. Wchnschr., 1907, XX, 123.	F	37	31	Epistaxis, during childhood. At 31 years, abdominal pain, vomiting, enlargement of abdomen. Later, chills and sweating.	32 × 16 × 12 cm. Weight, 3000 gm.	Extends a "hand-breadth" below costal margin.	Enlarged slightly.	.....
8	Marchand: München. Med. Wchnschr., 1907, LIV, 1102; also Resel: Beitr. z. path. Anat. u. z. allg. Path., 1909, XLVI, 241.	F	44	24	Pain in abdomen at 24 years. At 35 years, great weakness, myomatous uterus, ovarian tumor. Later, increased weakness, cachexia, hemorrhages in skin.	41 × 15 cm. Weight, 2720 gm.	24 × 26 cm. Extends 3 finger-breadths below costal margin.	Enlarged.	Brown
9	Brill, Mandelbaum and Libman: Am. Jour. Med. Sc., 1909, n. s., CXXXVII, 849.	F	42	21	At 21 years noticed abdominal tumor, sweating, hemorrhages of the skin, anæmia, emaciation, epistaxis, bleeding from gums and bowel, dyspnœa.	45 × 25 × 13 cm. Weight, 8100 gm.	35 × 30 × 12 cm. Weight, 3900 gm.	Enlarged slightly.	Brown
10	de Josselin de Jong u. van Heukelom: Beitr. z. path. Anat. u. z. allg. Path., 1910, XLVIII, 598.	F	12	7½	Enlargement of abdomen, weakness, bleeding from gums, attacks of syncope, vomiting.	Reaches to symphysis pubis.	Extends 2 finger-breadths below costal margin.	Not enlarged.	Yellow
11	Mandelbaum: Jour. Exper. Med., 1912, XVI, 797.	M	4½	3	Enlargement of abdomen, slight abdominal pain, epistaxis, increasing languor.	18 × 9.5 × 5 cm. Weight, 490 gm.	Extends 3 finger-breadths below costal margin.	Much enlarged.	Yellow
12	Wilson: Surg., Gynec. and Obst., 1913, XVI, 240.	F	27	12	Frequent digestive disturbance, anæmia, abdominal pain, œdema.	Weight, 5280 gm.	Extends 3 inches below costal margin.	.....	Slight
13	Downes: Med. Rec., 1913, LXXXIII, 697.	F	28	13	Enlargement of abdomen, loss of appetite, headache, emaciation, dyspnœa.	35 × 13.5 × 6.5 cm. Weight, 1813 gm.	Extends 1 inch below costal margin.	Not enlarged.	Pigmentation of face.
14	Niemann: Jahrb. f. Kinderh., 1914, LXXVIX, 1–10.	F	17 mo.	2 mo.	Never thrived; indigestion, pallor, enlargement of abdomen, œdema of eyelids and feet, low irregular fever.	Extends below level of navel.	Extends to 1 cm. above ant. sup. spine.	Enlarged slightly.	Pale-brown pigmentation.
15	Erdman and Moorhead: Am. Jour. Med. Sc., 1914, n. s., CXLVII, 213.	F	3½	14 mo.	Healthy infant, large spleen noted at 14 months. From this time nervous indigestion.	Extends to level of umbilicus.	Extends 2 finger-breadths below costal margin.	Inguinal glands enlarged.	Pale; no pigmentation
16	Herrman, Roth and Bernstein: Arch. Pediat., 1914, XXXI, 340.	M	14	4	Large spleen noted at 4 years, abdominal pain, epistaxis, hematemesis, bleeding from gums, asthenia.	27 × 13 × 10 cm. Weight, 1320 gm.	Extends 5 cm. below costal margin.	But little enlarged.	Pale; brown pigmentation of face.

Color of skin.	Blood Examination.	Family History.	Treatment.	Result and cause of death.	Histological Findings.	Remarks.
Leaden.	R. B. C.: 2,281,000 W. B. C.: 3,600, in last months.	Unknown.	Expectant.	Died. Tuberculosis, pulmonary and intestinal.	Spleen: Parenchyma replaced by large irregular cells with pale-staining cytoplasm in connective tissue spaces. Liver: Cirrhosis (?).	Condition unlike any known form of splenic hypertrophy.
.....	.....	One sister, enlarged spleen; three other children died of tuberculosis.	Expectant.	Died. Bronchopneumonia; no tuberculosis.	Spleen: Characteristic cells. Lymph glands: do.	No note on bone-marrow, liver or adrenals.
Slight jaundice.	R. B. C.: 1,300,000 After operation: W. B. C.: 20,000 Dif. count, normal.	No similar cases.	Splenectomy.	Living five months after operation.	Spleen: Characteristic cells. Lymph glands: do.	No note on other tissues. Case similar to Case 1.
Brown pigmentation, marked on face.	R. B. C.: 2,880,000 W. B. C.: 4,000 Hb.: 60%	One sister, enlarged spleen and liver.	Splenectomy.	Died three hours after operation.	Spleen: Characteristic cells. Lymph glands: do. Liver: Cirrhosis with do. Adrenal: A few do.	No note on bone-marrow.
Brown pigmentation.	At 15 years: R. B. C.: 5,000,000 W. B. C.: normal. Later: W. B. C.: 4,000 Hb.: 45%	Four out of six brothers and sisters had same condition.	Expectant.	Died. Exhaustion, pericarditis.	Spleen: Characteristic cells. Liver: do. Lymph glands: do.	.....
Brown pigmentation.	At 43 years: R. B. C.: 4,700,000 W. B. C.: 1,300 Later: W. B. C.: 800 Dif. count, normal. Hb.: 65%	One sister has large spleen; five children of parents well.	Expectant.	Died. Tuberculosis, pulmonary and glandular.	Spleen: Characteristic cells. Liver: do. Lymph glands: do. Bone-marrow: do.	Disease said to involve lymphatico-hematopoietic system, due to poisoning; possibly tuberculosis.
.....	At 37 years: R. B. C.: 4,200,000 W. B. C.: 7,000 Dif. count, normal. Hb.: 92%	.....	Splenectomy.	Living five months after operation.	Spleen: Characteristic cells.	Constant abdominal pain after operation. Liver still large.
Brown pigmentation.	"No leucocytosis."	No history of similar condition in family.	Expectant.	Died. Exhaustion.	Spleen: Characteristic cells. Liver: do. Lymph glands: do. Bone-marrow: do.	Ascites noted.
Brown pigmentation.	R. B. C.: 3,500,000 W. B. C.: 3,600 to 5,200 Dif. count, normal. Hb.: 35%	Brother of Case 5; four out of six brothers and sisters had the same condition.	Expectant.	Died. Fracture of skull.	Spleen: Characteristic cells. Liver: do. Lymph nodes: do. Bone-marrow: do.	More abdominal process than in Case 5. No tuberculosis.
Yellowish brown pigmentation.	R. B. C.: 4,700,000 W. B. C.: 3,800 Dif. count, normal. Hb.: 65%	Three sisters and one brother had large spleens; seven brothers and sisters well.	Splenectomy.	Living five months after operation.	Spleen: Characteristic cells.	Wassermann and von Pirquet, negative.
Yellow pigmentation of face.	R. B. C.: 2,208,000 W. B. C.: 5,000 Dif. count, normal. Hb.: 35%	One sister has large spleen; one sister has large liver; two children are well.	Splenectomy.	Died one day after operation.	Spleen: Characteristic cells. Liver: Cirrhosis and do. Lymph glands: do. Bone-marrow: do.	Wassermann negative. No tuberculosis.
Slight "jaundice."	R. B. C.: 5,200,000 W. B. C.: 4,800 Hb.: 80%	.....	Splenectomy.	Died 12 hours after operation.	Spleen: Characteristic cells.	Two other cases reported, thought by Marchand not to be Gaucher's disease.
Pigmentation of face.	R. B. C.: 3,840,000 W. B. C.: 1,400 to 900 Dif. count, normal. After operation: W. B. C.: 16,000	No history of similar condition.	Splenectomy.	Living 41 days after operation.	Spleen: Characteristic cells; not so extensive transformation as in other cases.	Probably a comparatively early case. Wassermann negative. Wedge-shaped thickening of conjunctiva.
Pale-brown pigmentation.	Blood said to be normal in R. B. C., W. B. C. and Hb.	.....	Expectant.	Died. Exhaustion.	Spleen: Characteristic cells. Liver: do. Lymph glands: do.	Wassermann positive. Extensive changes, very similar to those in our cases.
Pale; no pigmentation.	R. B. C.: 5,000,000+ W. B. C.: 10,000 Dif. count, normal. Hb.: 80%	One brother died with large spleen; two brothers well.	Splenectomy.	Living after 16 months.	Spleen: Characteristic cells.	Wassermann negative.
Pale; brown pigmentation of face.	R. B. C.: 3,000,000 to 4,000,000 W. B. C.: 5,000 Dif. count, normal. Hb.: 45%	One sister, next in age, had a large spleen: seven children well.	Splenectomy.	Living after six weeks.	Spleen: Characteristic cells.	.....

The *spleen* weighs 86 gm. and measures 13 x 5 x 4 cm. The surface has a mottled, patchy, grayish-pink color. The organ feels firm and its edges are rounded. The surface is smooth and glistening. The capsule is slightly thickened. On section the organ cuts easily and the splenic pulp is friable. The cut surface is rather moist and shows numerous red, slightly translucent areas, 1 mm. in diameter, surrounded by a soft, faint reddish-yellow peripheral zone that can be scraped out quite easily and resembles the material removed from the liver, although in the spleen it has a pinker appearance. There is no marked increase in the fibrous tissue.

The *pancreas* shows no pathological changes. The *kidney cortex* is slightly swollen and has a pale yellow color. The striations are poorly defined. The *adrenal glands* are considerably enlarged, each weighing 5.5 gm. On section a considerable amount of a brick-red fluid escapes from the medulla. The latter is large and prominent and has a pale yellow color. The cortex appears normal, though its yellow color is quite marked. In the mucous membrane of the stomach, near the pylorus and projecting 3 mm. above the surface, is a firm nodule 0.5 cm. in diameter, from which a gray mucoid material can be expressed. The intestinal mucosa shows congestion and a few small ecchymoses. The Peyer's patches are swollen. The appendix is rather large, but otherwise normal. The solitary follicles of both the small and large intestine are enlarged and surrounded by a narrow zone of congestion. The pelvic organs show nothing abnormal. There is a general enlargement of all the lymph glands, though the epitrochlear and other superficial nodes, except the inguinals, were not felt. They present a uniform appearance, being more or less bright yellow in color. They are quite firm and cut with a slightly increased resistance. On section a moderate amount of pale yellow viscid material escapes from the central part of most of the glands. The largest glands are near the head of the pancreas, measuring 1.5 x 2 cm. The thymus has an unusually pale yellow color, but otherwise is normal in size and appearance.

Microscopical Findings: *Heart.*—Many of the nuclei of the heart muscle are surrounded by a clear zone. Vacuoles of varying size, usually very small, are numerous in the muscle fibers. In some areas, where the fibers are cut in cross-section, the vacuoles are so numerous that the tissue resembles a markedly fatty liver. These vacuoles stain neither with Sudan III nor with osmic acid.

Lungs.—Most of the lung tissue appears normal. The air sacs contain a few desquamated epithelial cells. There is, however, a peculiar swelling of the cells of the interstitial tissue which gives them a finely vacuolated appearance. As indicated in the macroscopical report, the pleura over the lower lobe is thickened, and broad bands of loose connective tissue pass in, dividing the lung tissue into regular, well-defined lobules. The interstitial tissue is very much thickened and infiltrated with lymphocytes, swollen cells, many of which have a vacuolated protoplasm, and young connective-tissue cells. The connective tissue about the bronchi and the vessels is markedly increased. Surrounding the muscularis of some of the small arterial twigs there are several concentric rows of markedly swollen, pale, vesicular or granular cells, similar to, if not identical with, the large pale cells of the spleen and lymph nodes. The lumina of these vessels are often completely obliterated. The air sacs contain many large, irregularly round, faintly pink-staining, granular or vacuolated cells with a small nucleus, rich in chromatin; these resemble somewhat the large pale cells of the liver and spleen. They also resemble closely the swollen, partly degenerated cells in the air vesicles.

Liver.—The capsule is not thickened. The lobulation is well marked in some areas and obscure in others. In the former there is a considerable increase in the fibrous tissue of the portal spaces with extension into the lobule. The intralobular architecture is entirely obliterated, the normal arrangement of liver cells in columns, radiating from the central vein, being replaced by an irregularly distorted conglomeration of large polygonal or irregularly round, granular cells of two types. The cytoplasm of the predominating type stains deeper and shows coarse protoplasmic granules and numerous small vacuoles. The cells of the other type frequently appear to be inserted between those of the first, and are distinguished by their very faintly staining, finely granular or vacuolated cytoplasm. They suggest swollen endothelial cells, whereas the darker-staining cells resemble swollen transformed liver cells. In both cases the nucleus is relatively small, stains rather deeply, and may contain one or two definite chromatin granules. Although in most of the cells the cytoplasm is granular, in some there are many vacuoles, which are usually small, though large ones occur. In other cells the cytoplasm may contain vacuoles of various sizes; it may present a streaked appearance or may be concentrated into a small area in an otherwise vacuolated cell. No normal hepatic cells are present. A few elongated or oval cells with a finely granular or vacuolated cytoplasm are embedded in the fibrous tissue of the portal spaces, especially where there is considerable fibrosis.

Spleen.—The most striking change in the spleen is the replacement of the lymphoid cells by large cells separated into clusters and columns by very prominent sinusoids. The lymphoid cells and splenic pulp cells are present only about the Malpighian bodies, which are also being infiltrated with these large pale cells. The latter tend to group first in the center of the corpuscle. A few lymphocytes are occasionally present in or about the sinusoids. The capsule and trabeculæ are slightly thickened and strands of fibrous tissue extend into the parenchyma of the organ. The Malpighian bodies are diminished in number and show a striking tendency to be replaced by large cells—the process beginning in the center of the Malpighian body and progressing peripherally. These large, round, oval or polygonal-shaped cells usually have a faintly staining granular and vacuolated cytoplasm. The reticulum encloses clusters of these cells. Frequently strands of reticular fibrillæ occur between the individual large cells. Some of the large, pale cells lie free in the reticular spaces. They may contain two, rarely three, nuclei. A few of the large, pale cells contain red cells or nuclear fragments. This phagocytosis is not frequent. The endothelial cells of the sinusoids are markedly swollen and mitotic figures may occasionally be seen. All transitional stages occur between the large, swollen endothelial cells and the very large pale, finely granular cells lying free or attached to the wall of the sinusoids. Blood pigment is present, especially in the large, pale cells about the Malpighian bodies.

Pancreas.—Many of the cells of the islets appear swollen and granular and small vacuoles are frequent in the cytoplasm. In the interlobular connective tissue there are a few small foci of large, rounded, vacuolated, endothelial cells; otherwise nothing abnormal is noted.

Kidneys.—The capsule is not thickened and the interstitial tissue is not increased. The epithelial cells of the convoluted tubules are swollen; the cytoplasm is granular and often contains small vacuoles. The glomeruli are prominent. The cells in the capillary tuft tend to become swollen, and their cytoplasm is often distinctly vacuolated. Occasionally, two or more of these cells may become so much enlarged and filled with vacuoles that they appear identical with the large, pale cells of the spleen.

Adrenals.—In the cortex the cytoplasm is granular and is often undergoing a vacuolar or œdematous change, especially in the outer zone. The medulla is very much enlarged and is the seat of a peculiar change which, in some areas under the low power, gives it the appearance of adipose tissue, owing to the replacement of the medullary cells by large, irregularly rounded, granular or vacuolated cells embedded in a coarse reticulum. On higher magnification these large cells have a granular or vacuolated foamy

cytoplasm and a small nucleus; they seem to be identical with the large cells described in the spleen. In some areas the medulla has the appearance of a very wide-meshed, irregular reticulum, the spaces of which contain a granular or vacuolated cytoplasm more or less completely subdivided by cell outlines and containing deeply stained, scattered nuclei. The cells lie without the blood-vessels and sinuses, and usually fill the reticular spaces in which they occur. In some sections there are a few more or less compressed cords of medullary cells separated from the cortex by a larger or smaller zone of the large, pale, foamy cells.

Gastro-intestinal Tract.—Vacuoles are frequent in the epithelial cells of the mucosa and in many of the stroma cells. The epithelium of the intestinal villi has, for the most part, desquamated; the tunica appears œdematous and contains some polymorphonuclear leucocytes and lymphocytes. Large, pale, slightly foamy cells occur in the stroma between the glands. These are especially abundant between the glands of the appendix and resemble the large, pale cells of the spleen. In the cæcum the serous surface is partly covered by a flat layer of lymphoid tissue, within which are many large, pale granular cells, identical with those of the spleen and lymph nodes. Beneath the serosa and between the different layers of the small intestine small foci of similar large, pale cells occur.

The *thymus* is distinctly lobulated. The lymphoid cells have disappeared except in the immediate vicinity of, and where they radiate from, Hassall's corpuscles. Numerous large, pale, granular or vacuolated cells, similar to those of the spleen, are embedded in a wide-meshed reticulum. They occur singly and in clusters. None of these cells are seen in the capillaries or lymph sinuses. The *lymph glands* present a variable appearance, but in all of them there has been a more or less extensive replacement of the lymphoid cells by the pale granular cells described in the spleen. In some sections there are comparatively few of these large cells, and they are most abundant in the medullary portion of the node. In other sections practically all of the lymphoid cells have disappeared, giving the appearance of an endothelial tumor, except that the normal architecture and framework of the gland is still intact. The peripheral and medullary sinuses are easily recognized, and are more or less filled with large, pale, rounded cells. All intermediate stages between these two may occur. In some of the glands there are irregular bands of young cellular connective tissue in which vacuoles occur. The large, pale cells appear to develop first in the medullary part of the gland. Some of these cells show phagocytosis of red blood cells and leucocytes. In the later stages the cells appear in the lymphoid foci and in the peripheral sinuses. In the late stages the lymph and blood sinuses are very prominent and the lining endothelial cells show all transitions to the large, pale, vacuolated cells occurring in the spleen. Mitosis is occasionally seen in these endothelial cells. In other portions these cells appear to be closely related to the reticulum. They are usually rounded or polygonal in shape and contain a considerable amount of granular protoplasm, which tends to be vacuolated or foamy, and a rather small nucleus rich in chromatin. The cells are arranged in alveoli bounded by reticulum or by blood-vessels or sinuses. The connective tissue is not markedly increased in any of the lymph nodes, though in the larger glands the large, pale cells are separated into distinct lobules by strands of fibrous tissue. There is no blood pigment present. The large, pale cells infiltrate all of the lymphoid foci of the alimentary tract, but the lymphoid cells always predominate. This is especially well marked in the flattened mass of lymphoid tissue on the serous coat of the cæcum, in the solitary lymph follicles of the large and the small intestine, in the lymphoid tissue of the appendix and in minute lymph nodes near the intestine.

Special Microscopical Technique.—Examination of frozen sections of material fixed in formalin shows the presence of a homogeneous, slightly refractile substance in the large, pale granular or vacuolated cells. It fills the vacuoles in the protoplasm noted in the paraffin and colloidin sections. It is not as readily removed by ether as by absolute alcohol. This substance in the large, pale cells reacts in a peculiar but distinctive way to the fat stains. With scarlet red the large cells show many minute, faint orange-staining droplets. In some cells more of the dye is taken up; in others a few of the droplets take a deep orange-red color. The same results were obtained with Soudan III. In both cases the fat control section stained a deep orange-red. With Nile-blue sulphate the large cells took a faint violet, pale blue, or pink color, which in chromated sections changed to a deep blue, while the fat in the control section stained bright red and the fatty acid stained purple or blue. With osmic acid the homogeneous substance in the large, pale cells stained either faintly gray or not at all. It was stained black with the Weigert-Pal myelin sheath stain and was doubly refractive in many of the cells. Some of the large cells took a dirty, reddish-brown color with scarlet red. In the liver, spleen and lymph nodes there were scattered large, pale cells more or less filled with droplets of neutral fat. These were especially abundant in the thymus. The large cells, embedded in the periportal fibrous tissue of the liver were mostly filled with droplets, staining red with scarlet red. The cortical cells of the adrenal gland were more or less filled with red-staining droplets, after treatment with scarlet red, standing out in sharp contrast with the non-staining or pale orange droplets filling the large, pale cells in the medulla. In the kidney most of the large, pale cells in the glomerular tufts contained red-staining droplets after treatment with scarlet red, but did not stain with osmic acid. A few scattered droplets of neutral fat were present in the epithelium of the convoluted tubules. The vacuoles noted in the heart muscle did not stain with any of the fat dyes. After treatment with Ciaccio's and also with Bell's stain for lipoids, some lipoid droplets were present in the large, pale cells. In most of the organs, especially in the liver, spleen and lymph glands, there were all transitions between cells that did not stain at all and those which contained deep orange-staining droplets after treatment with scarlet red. These varying reactions to the different methods for the demonstration of fats and lipoids in tissues suggest the presence of some fat-like substance, within the large, pale cells, that may be in the process of transformation into neutral fat and possibly represent an intermediate stage between the latter and a closely bound molecule of proteid and fat.

CASE II.—On February 11, 1914, the mother of the former infant (Case I) brought to the out-patient department of the Harriet Lane Home another female infant, S. G., 5 months of age, and remarked that this baby had the same disease as her sister, who had died 20 months before. The similarity in appearance of the two infants was striking.

Past History and Present Illness.—The patient's birth was normal. She was exclusively breast-fed. She had always been thin and sickly, but presented no symptoms of any acute disorder. She was brought to the clinic because of her weak and emaciated condition.

Physical Examination.—The patient was much emaciated. She weighed 9 pounds. The temperature was 96.4° F. The skin had a grayish-yellow color. There was no general glandular enlargement. The right lung was clear. There was slight impairment and a few moist râles at the base of the left lung. The heart sounds were clear. The abdomen was full, measuring 14 inches in circumference. The superficial abdominal veins were dilated. The liver was enlarged and firm and extended 2½ inches below the costal margin, from the sixth interspace. The spleen was enlarged, firm in consistence, and reached 2½ inches below the costal margin, extending slightly below the level of the umbilicus. The cervical glands were palpable; the inguinal and axillary glands were slightly enlarged. The reflexes were normal, as were also the electrical reactions. Slight lateral nystagmus was noted.

The patient returned occasionally to the clinic, but her condition remained unchanged. In May the blood condition was as follows: Red blood cells, 3,024,000; white blood cells, 11,240; hæmoglobin, 65%. Differential count: Polymorphonuclear cells, 34%; lymphocytes, 60%; transitionals, 3.5%; eosinophiles, 1%; basophiles, 1.5%. The Von Pirquet and Wassermann tests were negative.

The patient was admitted to the Harriet Lane Home May 18, 1914, the condition being practically unchanged. On July 22, the temperature rose to 102° F., and continued irregularly elevated. In August a number of furuncles developed. In September a sharp rise in temperature was occasioned by an otitis media, secondary to a nasopharyngeal infection. The leucocytes varied from about 18,000 to 22,000, the differential count showing polymorphonuclear cells, 31%; mononuclear cells, 67%. On October 29, the patient was given a treatment with radium applied over the splenic area.

On October 21, some lymphatic glands from the neck and axilla were excised. Microscopic examination of the sections showed that a considerable number of areas of the gland were occupied by the large, round, oval endothelial-like cells, known to be characteristic of Gaucher's disease. This is the first time that a diagnosis of this condition has been confirmed during life, except by removal of the spleen.

On October 28, 1914, blood examination was as follows: Red blood corpuscles, 4,608,000; leucocytes, 6,480. Differential count: Polymorphonuclear leucocytes, 77%; mononuclear leucocytes, 21%; transitionals, 1%. The reduction in the number of leucocytes seemed to be directly due to the effect of the radium. There was, however, no marked change in the patient's condition. The temperature remained elevated. On November 1, a second treatment with radium was given. This was followed by a further fall in the leucocytes to 5560 per c. mm. Following this second radium application the patient became stuporous and toxic. Internal strabismus developed with nystagmus. The leucocytes were further reduced, on November 12, to 4980, and on December 2, to 2360. At this time the differential count showed: Polymorphonuclears, 37%; small mononuclears, 39%; large mononuclears, 19%; transitionals, 1%; myelocytes, 3%. The spleen seemed somewhat diminished in size, being felt 1½ inches below the costal margin. There was no improvement, however, and the child gradually became weaker and took her food badly.

Examination of the eyes by Dr. Powers showed the following interesting condition: Both fundi were pale, the region of the disk in each eye was white with no distinct margin. In the region of each macula there was a bright red spot, slightly larger in the left than in the right eye.

The patient continued to lose strength and died from exhaustion on December 24, 1914.

Autopsy.—The body is that of a greatly emaciated, white female infant, 61 cm. in length. The conjunctivæ and buccal mucous membrane are pale. The ribs and other bony structures of the body are very prominent. The abdomen is greatly distended. The lower edge of the liver and spleen can readily be seen through the abdominal wall. The abdominal muscles are very thin and there is practically no subcutaneous fat.

The pleural and pericardial cavities are not implicated.

The *thymus* on section presents the same characteristic appearance as seen in the lymph glands (see below).

The *heart* weighs 25 gm. The myocardium is reddish-brown, mottled with wavy yellowish-gray streaks.

The *lungs* are of a similar appearance. They are voluminous, contain air, have a delicate, smooth pleura and a pronounced lobulation. The lobules are separated by narrow, bluish-white, translucent lines, bordered on each side by a zone which is still more translucent. The center of the lobule forms the air-containing portion of the lung and is yellowish-pink.

The *spleen* is much enlarged. It weighs 100 gm. and measures 10 x 6 x 3.5 cm. Its capsule is delicate with a smooth and glistening surface. The consistence of the organ is increased and its edges are round. The parenchyma is mottled; small grayish and bright red areas about 2 mm. in size alternate with larger, patchy, yellowish-pink, frothy areas. On section the characteristic mottled appearance is more pronounced. The trabeculæ and the Malpighian bodies are inconspicuous. The frothy, yellowish, slightly sticky material encountered on sections of the liver occurs here also.

The *stomach, duodenum and pancreas* appear normal.

The *liver* is greatly enlarged. It weighs 420 gm. and measures 28 x 10 x 4.5 cm. It is of normal shape. The capsule is delicate and its surface is smooth and glistening. Through it a uniform yellowish-pink, opaque parenchyma is visible. The lobules can be made out as tiny pink spots surrounded by a yellow periphery. On sectioning, the knife adheres slightly and a frothy, yellowish, slightly sticky material can be scraped off. The parenchyma is putty-like in appearance and consistence. The cut surface is similar in appearance to the external surface. The gall-bladder contains a small amount of apparently normal bile. The bile-ducts present nothing abnormal.

The *adrenals* are enlarged. They weigh 8 gm. and measure 4 x 3.5 x 1 cm. Their appearance externally presents nothing of interest. On section the medulla is more yellow than usual.

Kidneys.—The cortex of the kidneys is slightly swollen and has a yellowish tint. The glomeruli and striæ are in places indistinct. The *pelvic organs* appear to be normal.

Intestines.—The Peyer's patches of the small intestine, especially near the ileo-cæcal valve, are enlarged. The lymph follicles are very translucent. Just near the ileo-cæcal valve the mucous membrane of the cæcum is congested. The rest of the cæcum and the large intestine present large, translucent, solitary follicles.

Lymph Glands.—All the lymph glands are similarly involved. They are enlarged, discrete and slightly firm. Externally and on section they have a uniform, frothy, yellowish-pink color. The glands about the pancreas and hilus of the liver are most involved. The posterior cervicals on the right side are somewhat different from the glands of other regions. They are enlarged, more juicy, and both externally and on section they have a more reddish-pink color.

The *aorta* is normal in appearance.

The *bone-marrow* is hyperplastic and of a yellow color.

Brain, Spinal Cord, etc.—In the pia-arachnoid of the frontal lobe is a small amount of translucent, gelatinous material; otherwise the brain and spinal cord show nothing abnormal.

The following additional tissues were removed for microscopical examination—in gross they presented nothing abnormal: the thyroid, submaxillary, salivary glands, hypophysis, various cranial and peripheral nerves, skin, striated muscle, various arteries and veins.

Microscopical Findings.—The microscopical findings in this case closely resemble those of Case I; a detailed description will therefore be omitted, and emphasis placed upon additional findings.

Lungs.—The lung tissue throughout presents a picture similar to that described in the right lower lobe of the first case. Many of the bronchi, arteries and veins contain a few large cells, identical in appearance with those found in the air spaces.

Spleen.—The characteristic large cell in this case is also found in the lumina of the arteries.

Pancreas.—Both the acinar and island cells appear slightly swollen and granular. They frequently contain vacuoles of varying size and shape.

Liver.—The cells of the first type in places show an imperfect trabecular formation and are undoubtedly to be considered as altered parenchymatous cells. Cells of the second type are also found in the intima and in the lumina of the portal vessels.

Adrenals.—The medulla shows the same changes as in the first case. It is rather difficult to determine exactly where the medulla stops and the cortex begins. This makes the medulla look unusually wide. In the adventitia of a large artery of the capsule there is a mass of the characteristic large cells. In other parts of the capsule masses of what appear to be young cells of the same type occur. They are smaller and have a darker pink cytoplasm, which is more granular and does not contain so many small, clear droplets. Many of these cells contain red blood cells. Cells representing all stages from this apparently young cell, which closely resembles the polyblast of connective tissue, to the typical large cell are seen in these masses of cells and also scattered in the meshes of the capsule.

Kidneys.—The characteristic large cell is frequently seen in the glomerular tufts, between the tubules and at times in the capillaries.

Gastro-intestinal Tract.—The parietal and cuboidal cells of the gastric tubules contain small vacuoles. A few of the characteristic large cells are seen scattered in the lower part of the mucous membrane. The tubular epithelium of the colon contains some small vacuoles, which are to be differentiated from those of the large goblet cells.

Thymus.—Most of the lymphoid cells, of both the cortex and the medulla, have been replaced by more or less closely grouped large cells similar to those in the first case. Only a few imperfect lymph follicles remain, and a sharp differentiation into cortex and medulla cannot be made.

Lymph Glands.—Glands taken from different regions of the body show an extensive replacement of the lymphocytes by a large cell, identical in appearance to that in the thymus. These cells are chiefly located in the medulla. In some glands the "Keimcentra" are very prominent and mitotic figures are frequent among the large lymphocytes within them. They also contain scattered large cells which closely resemble the characteristic large cell of the medulla, except that they contain nuclear fragments and red blood cells. These phagocytes are limited almost entirely to the "Keimcentra." There are no well-defined transitions between the proliferating large lymphocytes and the large, pale cells. Some of the large, pale cells are more or less filled with small, greenish-yellow pigment granules, especially in those areas where there is considerable congestion and hemorrhage. There is some patchy increase in young connective tissue. The endothelial cells of the vessels and sinuses are swollen, but there is no evidence of proliferation. The glands of the peritoneal cavity are more involved than the superficial glands.

Bone-marrow.—The fat is entirely absent and a large cell identical in appearance with the one in the spleen is present in large numbers.

Thyroid.—The acinar epithelial cells are swollen and project into the lumina as round or oval cells with a pale cytoplasm filled with droplets.

Submaxillary Glands.—The epithelium of the ducts and acini contains vacuoles.

Brain.—Scattered through the pia and the brain substance of both the cerebrum and the cerebellum are large cells, identical in appearance with the characteristic large cell of the spleen of the first case. These cells are most common in the neighborhood of the Purkinje cells. The greater part of the cytoplasm of the Purkinje cells is filled with small droplets, only a small zone of normal cytoplasm remaining about the nucleus. The cytoplasm of these cells resemble closely that of the characteristic cell mentioned above. The *hypophysis* shows no lesions.

Spinal Cord.—The anterior horn nerve cells have their cytoplasm filled with clear droplets. In the *spinal root ganglia* the bipolar cells have a pale nucleus and their cytoplasm is filled with small, clear droplets.

Nerves.—Nerves of various size and from various parts of the body show a vacuolization of their medullary sheaths.

The *skin, striated muscle, arteries and veins of all sizes,* and *tonsils* show no lesions.

DISCUSSION.—The origin of the characteristic large pale cells is not very clear. In structure, position and staining reactions they are identical with those described in the small group of cases of primary splenomegaly first reported by Gaucher, who at first considered them to be epitheliomatous cells; but at present this neoplastic theory has very little support. Some authors hold that they are endothelial cells, others that they are derived from the cells of the reticulum, and still others believe that they come from both. Recently, one author, Mandelbaum, has advanced the theory that they are derived from large lymphocytes.

In the present cases there is no evidence that the large cells are derived from any one particular tissue cell. On the other hand, there is good reason to believe that several different tissues may produce the same large pale cell. In some places there is strong evidence that they are derived from the endothelial cells of the lymph sinuses (Figs. 8, 10, 11). On the other hand, there are just as good reasons for believing that they arise from the cells of the reticulum (Figs. 2, 3, 4). In many areas the endothelium shows no change, while the reticular spaces are filled with large pale cells, many of which are closely related to the reticular fibers. This is particularly true of the spleen, where there is generally little change in the sinusoids, in marked contrast to the presence of the columns and clusters of large pale cells outside the sinuses. In some places small vacuoles were present in the cytoplasm of the large lymphocytes, and it is possible that some may develop into the large, pale granular cells; but no such transition was seen. In the liver the large, pale granular or vacuolated cells are most probably transformed hepatic cells. In certain places they are arranged in radiating columns. In some sections a crescent-shaped mass of finely granular, deep eosin-staining cytoplasm could be seen at one side of a large cell, suggesting a hepatic cell in which a small part of the normal cytoplasm had persisted, while the greater part had been changed by an infiltration of some homogeneous substance and the nucleus had become smaller. No normal hepatic cells were seen and, in this respect, the liver is identical with that in Niemann's case. Similarly, the young connective-tissue cells and fibroblasts may take up this lipoid substance and become transformed into some of these large pale cells, thus accounting for the appearance of the latter about small arterioles (Fig. 18), and of those embedded in the periportal fibrous tissue of the liver. The large cells in the glomeruli of the kidney may come either from endothelial cells or from reticular cells. At no place is there evidence of any neoplastic nature in them. A few mitotic figures were seen in some of the endothelial cells, but only in those attached to the vessel wall. The large cells were not seen free in the large vessels. It is primarily the endothelial cells lining the small lymph sinuses and the cells of the reticulum that become transformed into these characteristic

large vacuolated cells, and of these (in our cases) the reticular cells of the lymphadenoid tissue seem the most susceptible.

The disappearance of the substance within the large pale cells on treatment with absolute alcohol or ether, and its atypical fat-like reactions to the microchemical tests for fats and lipoids, leave very little doubt but that the large cells owe their size to the accumulation, whether it be degenerative or infiltrative, of a lipoid substance, the exact nature of which is unknown. This substance does not behave like fat; yet its reactions to neutral fat stains show that it is closely related to the fats. It resembles myelin. Apparently, it represents a lipoid substance arising from a perverted metabolism. The nature and mode of formation of this lipoid substance are obscure, but it is probably closely related to lecithin. Whether its accumulation in the large pale cells and in the parenchymal cells is due to a degenerative or to an infiltrative process cannot be determined with our present knowledge of the condition. The peculiar bilateral change in the medulla of the adrenal glands may play a very important rôle in this metabolic disturbance, resulting in the accumulation of the lipoid substance in all of the tissues, liver, heart, kidney, pancreas and connective tissue, apparently wherever fatty degeneration and deposits occur. In fact, there is considerable fatty degeneration either superimposed on this "lipoid metamorphosis" or representing an end-product of it. It may also be, as Schultze first suggested, that the spleen, which is said to play a not unimportant part in fat metabolism in some abnormal conditions, is largely responsible in these cases.

The names applied to this disease are innumerable and misleading, because they attempt to be descriptive terms. They fail to describe the new cases and the constant variations which are being added each year, and which should all be included in a term which would connote the causal factor. As this, however, is unknown at the present time, considerable confusion would be avoided if all cases were termed simply "Gaucher's disease," until more definite information concerning the nature of the process is obtained. As the process in this disease is a very general one and not specific for the spleen, the term "splenomegaly" is a misnomer. As more cases are described, a greater or less number of organs seem to be involved. At first it was thought that only the spleen and lymph glands were involved, but the liver was then added, and, more recently, the thymus and the bone-marrow. In our cases the medulla of the adrenal glands must also be added to this list, and it is to be noted that similar but less prominent changes were found in other organs and in the central nervous system. It is also very probable that the case described by Schultze, in which there was implication of the spleen alone, associated with a lipoidæmia, represents an earlier stage in the same process, inasmuch as the morphology, position and microchemical reaction of the cells were similar. Schultze showed that the sections of the spleen of his case reacted to the microchemical tests for fats and lipoids just as did the sections of the generally accepted cases of Gaucher's disease described by Risel and by Schlagenhaufer; and the same reactions were obtained in our case. Apparently, any disease in which the spleen, together with any other organ, shows numerous large, pale granular or finely vacuolated cells, giving the characteristic microchemical reactions for lipoids and showing a tendency to be widely and diffusely distributed, belongs to this group, and any attempt to limit the condition to any single organ or any single set of organs is largely arbitrary.

Accordingly, it would appear that Gaucher's disease is not primarily a disease of the spleen or of any other organ or set of organs, but is a generalized process due to a disturbance in fat metabolism, manifesting itself by lipoid metamorphosis, that is, by the more or less diffuse accumulation of lipoid material in many cells with the formation of characteristic large pale cells. This process is most prominent in the hematopoietic system, especially in the spleen and lymph nodes, organs that are said to play a not unimportant rôle in abnormal fat metabolism.

Summary.—It is quite evident that the characteristic lesion in these two cases is the widely diffused accumulation and proliferation of the large, pale granular or finely vacuolated cells, most prominent in the lymphadenoid tissues, but apparently involving more or less extensively the reticular cells and the lymph-vascular endothelial cells, the process being generally associated with localized accumulations such as have been described in the medulla of both adrenal glands. The process was equally marked in the lymph nodes as in the spleen and probably had begun simultaneously in both locations, other susceptible tissues being subsequently implicated. The large pale cell was also found in bronchi, arteries, veins, capillaries, glomerular tufts, scattered between renal tubules, in the mucous membrane of the stomach, in the capsules of various organs, in the pia, brain and in large numbers in the bone-marrow. The occurrence of vacuoles in the parenchymal cells of most of the viscera—including the heart, pancreas, kidneys—thyroid, submaxillary salivary glands, in the Purkinje cells of the brain, in the nerve cells of the anterior horn of the spinal cord, in the bipolar cells of the posterior root ganglion of the spinal cord, taken in conjunction with the negative results after the use of fat stains, indicates either a vacuolar degeneration or an accumulation of lipoid material in those cells as in the large pale cells, and suggests the presence of a very general pathological process, involving especially the lymphatic system. The phagocytosis was more marked and extensive in the second case than in the first. There was also more fibrosis, a greater proliferation of lymphocytes and more blood pigment than in the first case.

Conclusion.—The characteristic large, pale granular or finely vacuolated cell with its lipoid contents, the predominance of this cell in all of the organs of the hematopoietic system, the familial character of the two cases, the clinical history, the physical and pathological findings, leave no doubt but that they belong in the group of cases first described by Gaucher. It is true that our cases showed a unique implication of the medulla of the adrenal glands, that the Peyer's patches and the thymus were equally involved and that there was a much more general and diffuse distribution of the character-

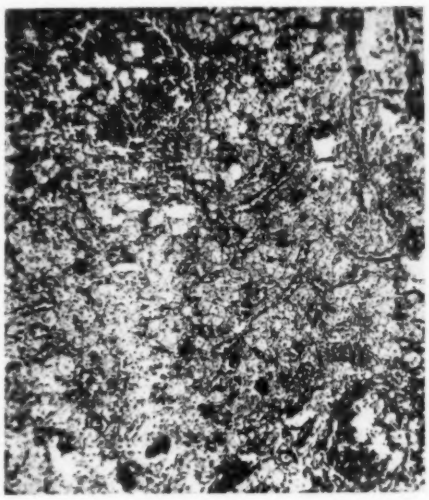


FIG. 1.

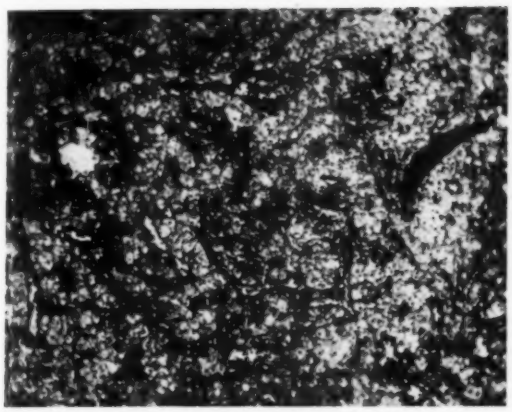


FIG. 2.

FIG. 3.

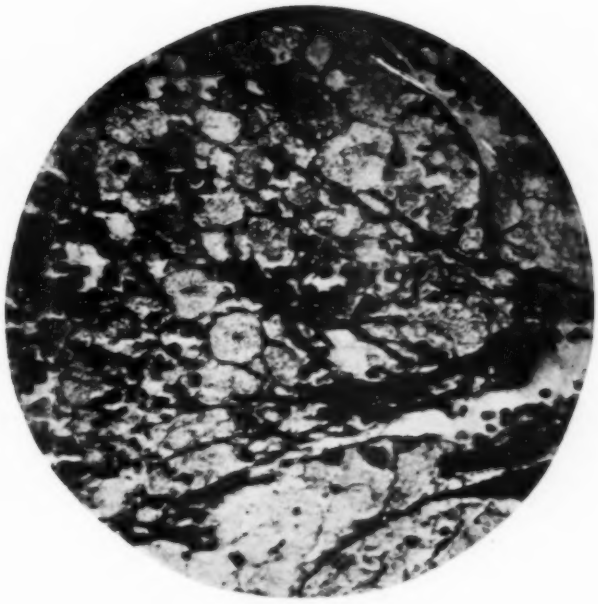


FIG. 4.

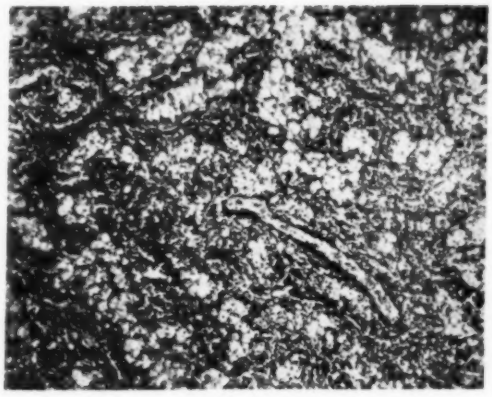


FIG. 5.

FIG. 6.

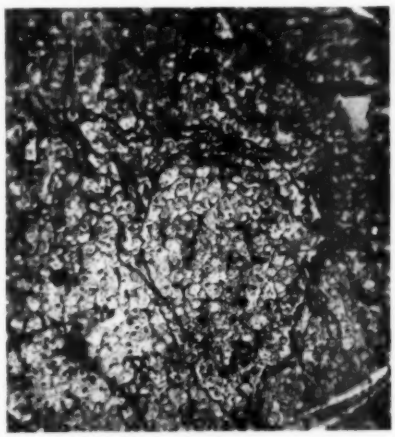


FIG. 7.

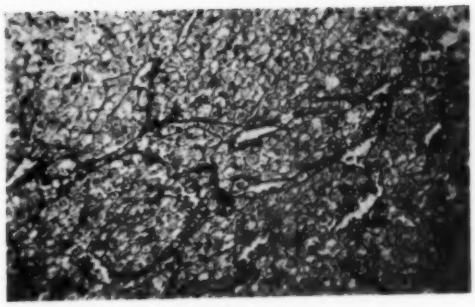


FIG. 8.

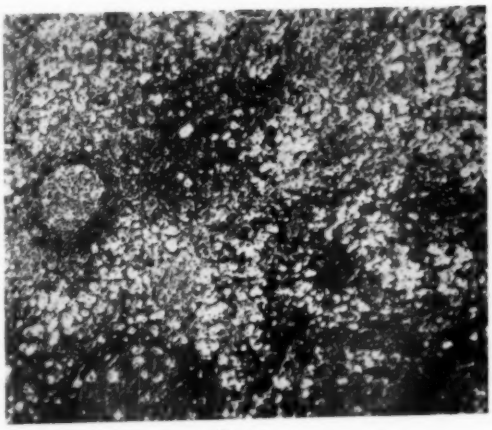


FIG. 9.

FIG. 10.

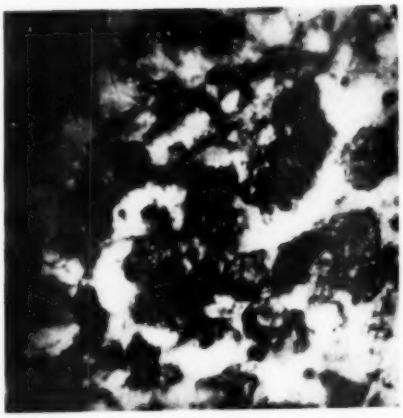


FIG. 11.

FIG. 12.

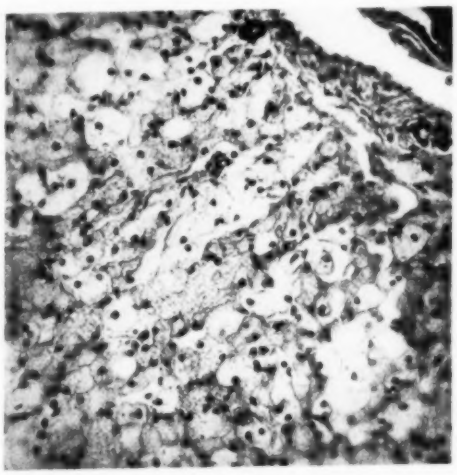


FIG. 13.

FIG. 14.

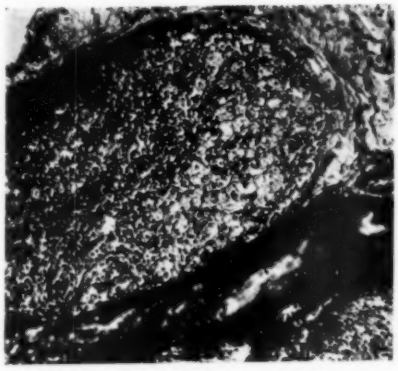
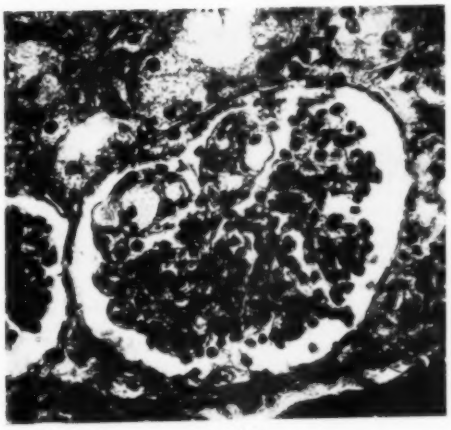


FIG. 15.



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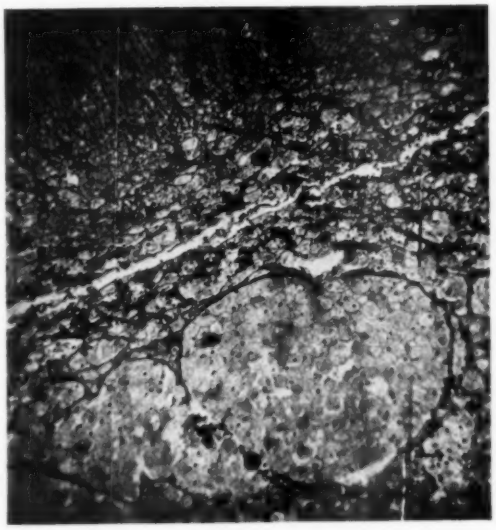

FIG. 17.

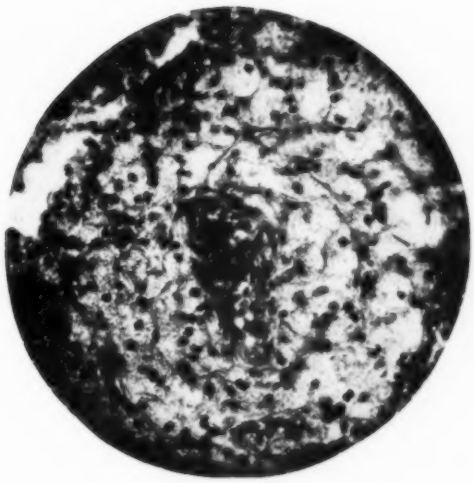

FIG. 18.

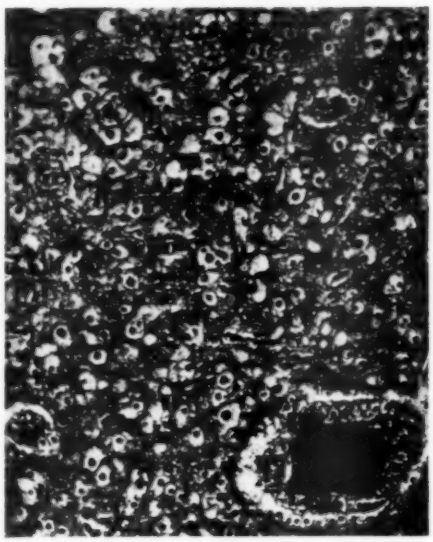

FIG. 19.

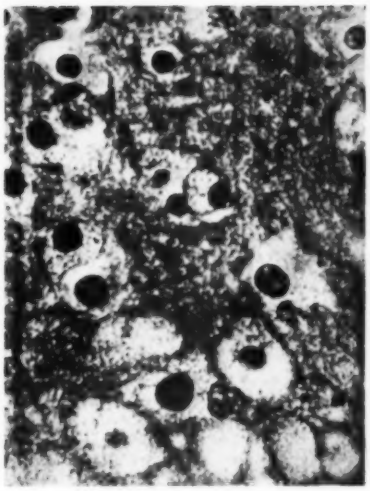

FIG. 20.

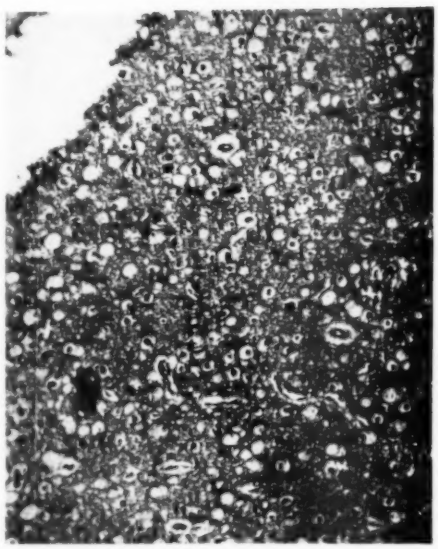

FIG. 21.

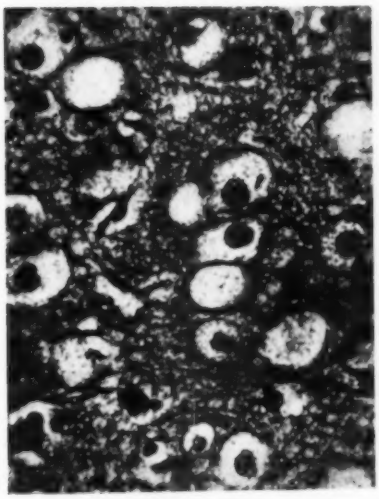

FIG. 22.

istic large cells; but this may be a manifestation of one and the same process, which in infancy is apt to be more rapid and widespread, as has been suggested by Niemann (see table).

FINAL SUMMARY.—In this report we have presented the cases of two infants, sisters, who did not thrive from birth and died, one at 11 months, the other at 15 months of age, from gradually increasing weakness. The most striking clinical feature was the great enlargement of the spleen and liver. The blood picture was that of a moderate anæmia. The leucocytes were rarely increased, and for the most part were markedly reduced in number. The skin in both cases had a peculiar yellowish-brown hue, more marked on the face and exposed surfaces. In one case the diagnosis was confirmed during life by the examination of an excised lymph gland. Microscopically, in both cases nearly all the organs were found to contain large, pale, granular or finely vacuolated cells, in which there was a peculiar refractive substance having the chemical and staining properties of lipoid material. These cells are apparently identical with those described by Gaucher, and later by a number of observers, in the condition called "Gaucher's disease." Our own cases and that of Niemann are the only ones in which the disease has been reported in infancy. The observation of cherry-red spots in the maculæ of Case II, in view of the presence of similar cells in the nervous tissues of cases of amaurotic family idiocy (Figs. 21, 22), lends additional interest and suggests the possibility that the essential degeneration in the latter condition may be of a similar character.

DESCRIPTION OF PLATES.

FIG. 1.—*Spleen* (× 65). Iron hematoxylin stain. Shows the relative disappearance of the lymphoid cells in the pulp and the presence of many pale granular or vacuolated cells between the sinusoids. Note the similar large, pale cells within the Malphigian bodies, also the prominence of the endothelial cells of the sinusoids.

FIG. 2.—*Spleen* (× 70). Iron hematoxylin stain. Shows the distended sinusoids separated by columns and nests of large, pale, granular cells. This represents a typical section of the splenic pulp.

FIG. 3.—*Spleen* (× 65). Bielschowsky silver method for demonstration of the reticulum. Shows the general architecture of the spleen with the well-marked sinusoids, the intervening large, pale cells and their intimate relation to the reticulum.

FIG. 4.—*Spleen* (× 480). Bielschowsky stain. Shows the character of the large, pale cells and their intimate relation to the reticular fibers.

FIG. 5.—*Lymph Gland* from Case I (× 70). Hematoxylin and eosin stain. Shows columns and nests of large, pale cells imbedded in the lymphadenoid tissue. Compare with Fig. 9.

FIG. 6.—*Lymph Gland* (× 70). Hematoxylin and eosin stain. Shows in one portion the large cells just appearing; in another the complete replacement of lymphoid elements by the same.

FIG. 7.—*Lymph Gland* (× 65). Iron hematoxylin stain. Shows the complete replacement of the lymphoid cells by the large, pale, finely vacuolated cells which are enclosed in the reticular spaces.

FIG. 8.—*Lymph Gland* (× 70). Iron hematoxylin stain. Shows the large, pale cells apparently arising from the endothelial cells lining the sinuses.

FIG. 9.—*Lymph Gland*, from Case II (× 65). Hematoxylin and eosin stain. Shows the presence of the large vacuolated cells in clusters and isolated in the lymphadenoid tissue. Note the presence of these cells in the germinal follicles, some showing phagocytosis.

FIG. 10.—*Lymph Gland* (× 480). Iron hematoxylin and eosin stain. Shows the character and location of the large, pale cells. Some of these cells are still attached to the wall of the sinus.

FIG. 11.—*Lymph Gland* (× 480). Iron hematoxylin and Van Gieson's stain. Shows the ragged, irregular outline of some of the large cells, the extension of their protoplasmic processes into the reticulum and the apparent origin of some of the cells from the reticulum.

FIG. 12.—*Liver* (× 70). Iron hematoxylin stain. Shows the fibrosis, the distortion of the intralobular architecture, and the absence of normal hepatic cells.

FIG. 13.—*Liver* (× 260). Iron hematoxylin stain. Shows the character of the parenchymal cells. Note the pale and the finely vacuolated darker types, also the absence of normal liver cells.

FIG. 14.—*Thymus* (× 80). Iron hematoxylin stain. Shows three Hassall's corpuscles, each surrounded by a zone of lymphocytes and columns and nests of large, pale, granular cells.

FIG. 15.—*Lymph Follicle in Intestinal Submucosa* (× 90). Hematoxylin and eosin stain. Shows the presence of the large, finely vacuolated cells to one side of the lymphoid mass.

FIG. 16.—*Kidney* (× 370). Iron hematoxylin stain. Shows a glomerulus. Note the characteristic large, pale, granular cells in the capillary tuft.

FIG. 17.—*Adrenal* (× 80). Iron hematoxylin stain. Shows the inner portion of the cortex and part of the medulla. Note the large masses of pale, granular cells inclosed in the reticular spaces of the medulla, the smaller, more scattered foci and the numerous red blood cells (stained black).

FIG. 18.—*Wall of a Small Blood-vessel in the Lung* (× 340). Hematoxylin and eosin stain. Shows a zone of characteristic large, pale, granular cells surrounding the wall of the vessel.

FIG. 19.—*Brain* (× 160). Iron hematoxylin and eosin stain. Shows the cortex of the cerebrum with the characteristic large, pale, granular cells. Note the apparent origin of these cells from the vessel endothelium.

FIG. 20.—*Brain* (× 450). Iron hematoxylin and eosin stain. Shows the cortex of the cerebrum with the characteristic large, pale, granular cells.

FIG. 21.—*Brain of Amaurotic Family Idiocy* (× 160). Hematoxylin and eosin stain. Shows the cortex of the cerebrum with large, pale, granular cells. Note the close resemblance of these to the cells in Fig. 19.

FIG. 22.—*Brain of Amaurotic Family Idiocy* (× 450). Hematoxylin and eosin stain. Shows a portion of the cortex of the cerebrum with the large, pale, granular cells. Note their close resemblance to the cells in Fig. 20.

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PLEURAL EOSINOPHILIA.

WITH REPORT OF A CASE.

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INCIDENCE.

Eosinophile pleural effusions have been recorded in 68 cases. Sixty-three of these have been assembled and analyzed by E. Schwarz[1] in his recent monograph on the general subject of eosinophilia. In addition to these, cases have been reported by Baur,[2] Kipp,[3] and Mosny and Portocalis.[4] These instances of the presence of eosinophile cells in pleural effusions are few indeed in comparison with the great number of effusions which have been examined during the 15 years that have passed since Widal and Ravaut[5] called attention to the clinical significance of pleural cytology. This figure, however, cannot be taken to indicate the actual incidence of pleural eosinophilia. It may be assumed with certainty that many pleural fluids have not been examined microscopically, and that relatively few of them have been stained with polychrome dyes, proper for the demonstration of eosinophiles. The case to be reported almost escaped recognition because of a temporary failure to apply an eosin-containing stain, and it serves as a text for calling attention to the knowledge which will be gained by the use of polychrome stains in the routine study of pleural effusions. Pleural eosinophilia, nevertheless, is a comparatively rare condition. Its incidence, as determined by investigators applying constant methods to cases in series, is about 1 to 5 per cent of all cases of pleural effusion.

Pleural eosinophilia following lobar pneumonia, as in the instance which is the subject of this communication, has been

TABLE I.

Summary of Cases of Postpneumonic Pleural Eosinophilia.

Author.	Etiology.	Day of puncture.	Red blood cor.	% Eosinophiles.	% Poly-neutro.	% Lymphocytes.	% Endothelial.	Remarks.
Barjon & Cade.[6]	Postpneum.	21,26	Numerous.	46,46	22,11	16,5	15,10	Animal inoculation negative.
Sandomirsky.[7]	"	24,27	.....	20,13	69,24	9,54	....	
Widal & Faure-Beaulieu.[5]	"	3,5,9,10	5900,2700	60,52,65,24	10,8,1,1.9	3,6,6,4	23,31,18,16	Some mast-cells.
		19,22,26	.....	72.82,85,76	0.5,1.5	1,1.8,1	21,12,7	Enormous toxicity.
		31,34,56,69	730,1960	2	2,5.7	2,71	7,17,18	Eosinophiles in blood, 3% to 16% to 0.1%.
Malloizel.[9]								
Obs. XLV.	"	9,15,18	Present.	A few at first, then many, then none.	....	Scanty.	....	
Obs. XLVI.	"	1,8	"	"	....	Abundant.	....	
Obs. XLVII.	"	8,11,22	Fluid at first purulent; then hemorrhagic.	None at first, then many.	Many.	Few.	....	
Obs. XLVIII.	"	1 month.	Many.	Many.	None.	Many.	....	Not tuberculous.
Mosny, Dumont, & Saint-Girons.[10]	"	6,7,9	.....	0,3,4	73,80,15	1.5,0.27,15	25,20,58	Fluid (1) purulent.
		11,13,16	.....	28,20,51	56,14.7,10	12,6,27	26,70,56	(2) Sero-purulent.
		18,21,23	.....	74,85,81	11.1,3,1.5	1,0,0.5	39,30,14.7	Sterile, with 11% mast-cells.
		25,27	.....	78.5,86	0.5,0.5	0,0	6.5,10.8	Blood, 2.5–11% eosinophiles.

recorded in eight cases. Of the 68 cases mentioned in the preceding paragraph, eight were of metapneumonic occurrence, giving approximately 12 per cent as the special incidence of postpneumonic pleural eosinophilia among all eosinophile pleural effusions. The findings in these cases are shown in Table I.

REPORT OF CASE.

J. A. N., white, male, aged 30 (Gen. No. 101461, Medical No. 33908), was admitted to The Johns Hopkins Hospital on March 20, 1915, to the medical service of Dr. T. C. Janeway.

The patient was a sailor whose health had always been robust. Since the age of 16, he had lived on ship-board, sailing frequently in the tropics. He had never suffered from any severe acute illness and had not acquired any tropical disease. Gonorrhœa eight years previously and periodic excesses in drinking alcohol were the only other significant facts in his past history.

He complained of "pain all over, sick stomach, and spitting blood." The history of the illness which caused him to come to the hospital was a typical account of the onset of a lobar pneumonia. When he entered, on the fourth day of his illness, he had consolidation of the entire right lung. His temperature was 105° F.; respirations 40 per minute. The results of the special examinations were as follows:

Blood: (March 20th) R. B. C. 5,032,000. Hb. 85 per cent. W. B. C. 11,000. The differential count, with Wilson's stain, showed polymorphonuclear neutrophiles 93 per cent; mononuclears 7 per cent. No eosinophiles were seen in counting 250 cells. The blood culture was negative, but a culture from material obtained by puncture of the lower lobe of the right lung yielded a pneumococcus of Group II. A similar pneumococcus was grown in pure culture from the sputum. The Wassermann test was negative. Chlorides were absent from the urine. No tubercle bacilli were found in the sputum. The feces were examined frequently for ova and parasites, but none were found.

The temperature remained between 103° and 105° F. until March 23d, the seventh day of the disease, after which it gradually declined. For the next seven days, however, the temperature remained between 99° and 100° F., with the pulse proportionately accelerated, while the respirations were from 20 to 25 per minute. During this time, the signs of resolution began to supersede those of consolidation. The leucocyte count, which had been 25,000 became 14,000 on March 27th. No eosinophiles had been seen in the differential counts up to this time. The percussion note remained dull at the right base; and as empyema was suspected, the pleural cavity was aspirated on March 29th.

Thoracentesis I.—Five hundred cubic centimeters of a cloudy, amber fluid were withdrawn. This fluid clotted readily and had a specific gravity of 1015; it contained 40 grams of protein and 2.5 grams of chlorides per liter. Cell count: White cells, 580 per cu. mm.; red corpuscles, 2000 per cu. mm. Sediment of this fluid stained with methylene blue showed that the predominant cell was the "small mononuclear." No bacteria were seen. Cultures of this fluid remained sterile, and a guinea-pig inoculated with a considerable amount of the sediment was not affected.

Within a week after the aspiration of the fluid, the patient's temperature became normal, and remained so. The signs of consolidation gradually disappeared over most of the right lung, except over a small area in the interscapular region, while the dullness at the right base persisted. A second aspiration of the right pleura was performed on April 5th.

Thoracentesis II.—Twenty cubic centimeters of turbid yellow fluid were obtained. This fluid clotted quickly. The white cells numbered 600 per cu. mm., showing a predominance of eosinophiles when stained with Wilson's stain. The differential count showed a significant contrast with that of the blood, the leucocytes of which numbered 11,200 on the day of the aspiration.

Type of cell.	Percentage in pleural fluid.	Percentage in blood.
Polymorphonuclear neutrophile	6	72
Polymorphonuclear basophile	0	5.6
Eosinophile		
Polymorphonuclear	44	1.2
Mononuclear	1	0
Small Mononuclear	30	9.6
Large mononuclear	16	7.2
Transitional	2	4.4
Endothelial cells	1	0
Totals	100	100.00

Cultures and inoculations with this fluid were negative.

It became evident that the pleura was thickened over the right base, with little or no fluid remaining in the chest-cavity. A radiograph (Plate No. 29060), taken on April 16th, showed: "Mediastinitis. Extensive infiltration of both lungs. Patchy consolidation of the upper lobe of the right lung, with thickened pleura over this lung." It was the opinion of Dr. Baetjer that these changes were largely postpneumonic, and could not be called tubercular. Tuberculin tests (Calmette) were negative.

On April 10th, the right pleura was again tapped. At this time the blood showed W. B. C. 7500, with 15 per cent of eosinophiles.

Thoracentesis III.—Fifteen cubic centimeters of yellow turbid fluid, which clotted almost immediately. A sp. gr. determination and cell count were not made. The hydrogen-ion concentration of this fluid was $10^{-7.5}$ (Dr. Levy)—practically a neutral reaction. Differential count. Wilson's stain. 300 cells counted.

Type of cell.	Per cent.
Polymorphonuclear neutrophile	5.6
Polymorphonuclear basophile	0.3
Eosinophile	
Polymorphonuclear	46.0
Mononuclear	1.0
Small mononuclear—granular	2.3
non-granular	39.0
Large mononuclear	1.6
Endothelial cells	1
Unclassified (degenerated cells)	3.2
	100.0

With Ehrlich's stain the differential count was:

P. M. N. 15 per cent.
P. M. E. 40 per cent.
S. M. 40 per cent.
L. M. 5 per cent.

SPECIAL STUDIES OF THE CELLS OF THE PLEURAL FLUID.

When treated with ammonium sulphide for the "iron-reaction" in the granules of the white cells, according to the method of Barker,[11] smears showed that nearly all the coarsely granular cells exhibited dark brown to black granules. Forty per cent of the white cells gave this reaction—a percentage about equal to that of the eosinophiles present in the fluid.

Oxydase reaction: Smears treated with β-naphthol and dimethyl-paraphenylendiamin, and counter-stained with aqueous saffranin, showed the violet-black granular oxydase reaction in 59 per cent of the white cells. Obviously, this included some of the mononuclear cells other than the mononuclear eosinophiles.

The patient improved steadily, the pulmonary signs gradually clearing. He was discharged on April 20, 1915.

On May 17th, he was seen when he landed from a cruise during which he had served as stoker on a steamship. He looked well and had gained weight. There was slight dullness at the right base, but no signs of pleural effusion. His leucocytes were 7900 per cu. mm., with only 1.5 per cent of eosinophiles, and a practically normal differential count. No mononuclear eosinophile cells were present in the blood at this or any other time.

DISCUSSION OF CASE.

This case presented two metapneumonic phenomena, namely: a pleural effusion and eosinophilia of the pleural fluid, together with blood-eosinophilia. The details of these conditions have been described with the report of the case; a discussion of their significance will be taken up in the succeeding paragraphs.

Small serofibrinous pleural effusions are common in pneumonia. Such effusions have been found in 65 per cent of a series of cases studied by puncturing the pleura.[12] Significant metapneumonic effusions, large enough to give physical signs (400 cc.), occur in 5 per cent of the cases.[13] In this case, the exudate was straw-colored, with sp. gr. 1015, albumin 40 grams per liter, 600 white cells and 1000-2000 red cells per cu. mm. It clotted quickly. Its reaction was neutral, with an H-ion concentration of $10^{-7.5}$, which eliminates any chemical abnormality which may affect the staining reaction of the cells of the exudate. The fluid was non-toxic when injected into guinea-pigs, was sterile when cultured, and did not produce tuberculosis in the animals into which it was injected. Corroborative of the non-tuberculous nature of the exudate, was the fact that at the time of the removal of the fluid, the patient gave no reaction to the 1 per cent and 5 per cent tuberculin conjunctival tests. The cytology of these exudates is variable; usually the polymorphonuclear leucocyte is predominant; rarely, as in this case, the eosinophile is the chief cell.

Eosinophiles in the blood in lobar pneumonia are usually rare before the crisis, begin to appear shortly before or after the crisis, and rise to normal or increased numbers after the crisis. The noted cases of postcritical eosinophilia in pneumonia seem to indicate that the condition is partially independent of the local process and the fever, but that it is in some way associated with the reaction by which the organism regains health. It seems likely that some substance which stimulates the production of eosinophiles is produced in the diseased tissues. The eosinophiles in the blood in all these cases have been of the usual polymorphonuclear type of α-cell.

Pleural eosinophilia after pneumonia, which has been observed eight times, has always been associated with blood eosinophilia, but differs both in degree and in exact morphological type of the eosinophile cell which appears in the blood. The local eosinophilia may amount to from 40 to 80 per cent of the cells of the pleural exudate, while the blood-eosinophilia is generally of a lower degree, in this case 47 per cent for the former as compared with 15 per cent for the latter. In the absence of any other reason for eosinophilia, the hemic and pleural eosinophilia must be attributed to a common cause associated with the specific disease—an eosinotactic substance, the nature of which will be considered later.

The eosinophiles in the pleural exudate were very different from those present in the blood. In addition to the usual multilobed eosinophile, this fluid contained mononuclear eosinophiles, whose characteristics are shown in the accompanying illustration (Fig. 1 (1)). These mononuclear eosinophiles varied in diameter from 11 to 15μ; the nucleus was round, filling about one-half of the cell; it was dense, but not so dense as the nucleus of the lymphocyte, and contained masses of chromatin of varying size and shape. The cytoplasm was faintly basophilic and contained large refractile granules, which stained intensely red with eosin, gave the oxydase reaction, and showed a brown reduction of ammonium sulphide, when tested for the "iron-reaction," characteristic of eosinophiles. These cells looked like the typical eosinophilic myelocyte.

Two main theories of the origin and nature of these cells have been proposed. Ehrlich[14] and his followers, applying their theory of the myelogenous origin of eosinophiles, regard these cells as emigrated blood-eosinophiles, which have assumed a mononuclear form in the process of karyorrhexis. Dominici[15] and Widal[16] have held the opinion that these eosinophiles arise locally in the diseased structure by myeloid metaplasia of lymphoid tissue. The occurrence of mononuclear eosinophiles in nasal polyps and numerous other pathological and experimental eosinophilic lesions, is strong evidence in favor of the supposition that they have a local origin. Schwarz[1] sums up the controversy by saying that while the bone-marrow usually plays the chief rôle in the increase of the eosinophilies, the fixed mesenchymal cells may also give rise to them. In the embryo, hematopoietic mesenchyme is widely distributed. In the adult the bone-marrow becomes the chief seat of blood formation, but throughout the body myeloid rests remain in a state of latent function. This tissue, present in the spleen, lymph-nodes, intestines, and in the adventitia of blood-vessels, resumes its function when acted upon by the proper stimulus, *e. g.* an eosinotactic substance, and produces any or all of the myeloid cells.

Among the mononuclear cells of this fluid were a number of granular cells which could not be classed with either the ordinary lymphocyte or myelocyte. These cells gave typical oxydase reactions, and had characteristics suggesting a myeloid origin, similar to that proposed for the eosinophiles. The other elements of the mononuclear group (called by Kipp[3] and Pappenheim "Group L"), were typical lymphocytes and endothelial cells.

Occasionally, small basophilic cells with "budding nuclei" were found. These were difficult to distinguish from normoblasts (Dr. W. Baetjer) when the origin of the specimen was not known. Such a cell is shown in Fig. 1 (8).

Basophilic leucocytes formed 0.3 per cent of the cells (Fig. 1 (7)). In 1913, Mosny and Portocalis[4] found such basophiles in a pleural effusion and described their discovery as "un élément nouveau." They are probably mast-cells from the pleura, and have no special significance.

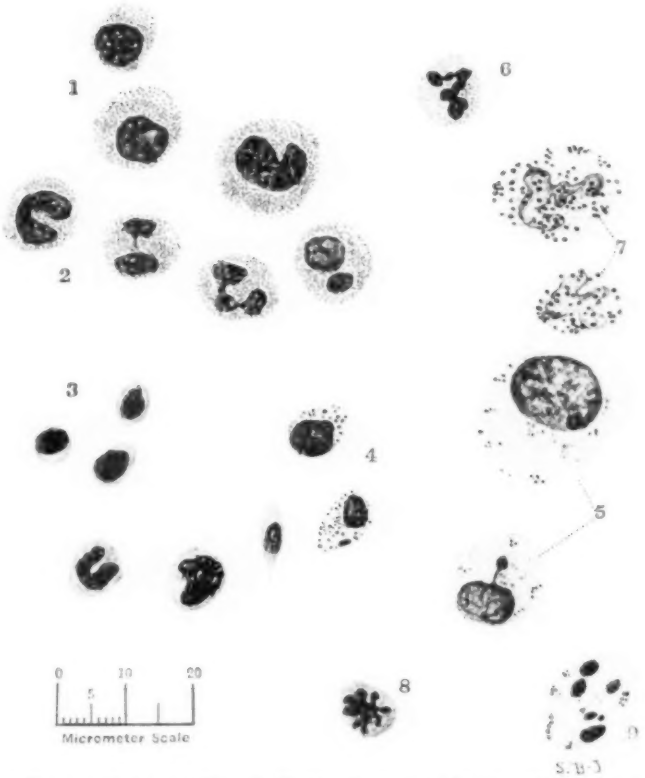

FIG. 1.—Cells of Pleural Fluid, Drawn to Scale with Camera Lucida. Wilson's Stain.

1. Eosinophiles—mononuclear.
2. Eosinophiles—polymorphonuclear.
3. Mononuclears—lymphocytes.
4. Mononuclears—with polychrome granules.
5. Mononuclears—endothelial cells.
6. Polymorphonuclear neutrophile.
7. Polymorphonuclear basophiles.
8. Mononuclear cell with budding nucleus.
9. Degenerated cell.

Polymorphonuclear eosinophiles formed 5.6 per cent of the cells of this exudate. They are without significance here, except as an indication of the absence of any very acute inflammation at the time of the aspiration of the pleura.

Occasionally, bizarre elements were found, large vacuolated cells containing polychromatophilic granules and masses of chromatin, which took a deep stain. There were evidently degenerated cells, showing a striking contrast to the fresh-looking mononuclear eosinophiles (Fig. 1 (9)).

ETIOLOGY.

The etiology of pleural eosinophilia has never been elucidated. The most positive inference deducible from the reports of the condition is that the substance determining the presence of eosinophile cells in effusions is a property of the exudate itself, and is independent of the bacterial, mechanical, or other cause of the effusion. Pleural eosinophilia has been found in pleurisy due to the following causes:[1] trauma, tuberculosis, sepsis, typhoid fever, syphilis, pleuropericarditis, pneumonia, polyarthritis, nephritis, pulmonary gangrene, hemorrhagic infarct of the lung, endothelioma, septic endocarditis, gonococcal sepsis, myocarditis, cardiac insufficiency, puerperal sepsis, neoplasm, influenza.

From this list of heterogeneous diseases involving the pleura which have been associated with eosinophilic exudates, no etiological conclusions can be drawn. The list, however, serves to show that the eosinotactic substance is independent of the local cause of the pleural effusion. Weidenreich[11] and others have considered that the erythrocytic content of the exudate determined the degree of the eosinophilia. In conclusive opposition to this may be taken the investigations by which it has been shown that eosinophilic granules have little in common with hemoglobin. Staübli[11] has demonstrated that cells which actually ingest red corpuscles do not form eosinophile granules. If, however, Weidenreich's hypothesis had not been disproved, the fact that one-third of the exudates reported contained a minimal number of red blood-corpuscles would indicate the inadequacy of his explanation. In a similar manner, attempts to relate the eosinophilia to the presence of other cells in the exudate have been unsuccessful. The cytological formulæ of the exudates are too inconstant to serve as a basis for etiological deductions. The sterility of the exudate or its bacterial content has no influence upon the presence or absence of eosinophilia. As a rule, bacteria or their products tend, on the contrary, to exert an anti-eosinophilic action. Widal and Ravaut[3] have shown that most of the eosinophilic exudates are sterile, but that some of them exhibit an unusual degree of toxicity for laboratory animals. The experiments on which these conclusions are based are negligible as regards their bearing on the question of toxicity, but they point in the direction in which is to be sought the substance which stimulates the production of this type of eosinophilia. Since all other factors have been eliminated, the chemical properties of the exudate appear as the important element in the reaction. Schwarz[1] has advanced the hypothesis that protein split products in the exudate form the eosinotactic substance which produces the local or pleural eosinophilia (histoeosinophilia) together with its associated blood-eosinophilia (hemeosinophilia). In an exudate undergoing resorption or, at least, becoming altered by the action of immune ferments, split products of proteins are formed, and these substances are demonstrable in the exudates as proteoses and peptones. The experimental work on anaphylactic eosinophilia and eosinophilia in helminthiasis has shown that the split products of proteins are capable of producing both local and general eosinophilia. As ferment action in any exudate, regardless of the immediate cause of the effusion, produces these eosinotactic bodies, this hypothesis is the only one broad enough to include all the known factors in the occurrence of pleural eosinophilia. The hypothesis, however, is only partially established by experiment, but it seems especially worthy of consideration, as it correlates a known mild process with a known biological healing-reaction, and as it explains how pleural eosinophilia may occur in many different forms of pleurisy.

DIAGNOSTIC SIGNIFICANCE.

The eosinophilia of pleural effusions occurs in so many diverse conditions that it cannot be correlated with any special morbid process. The small number of tuberculous pleurisies in the cases of pleural eosinophilia has been pointed out by several authors. For instance, Widal and Ravaut[3] found one instance of eosinophilia in fifty tuberculous effusions. Aside from the suggestion afforded by this, that a pleural effusion containing eosinophiles is usually not tuberculous, no diagnostic significance can be attached to the presence of an eosinophile exudate.

PROGNOSTIC SIGNIFICANCE.

Eosinophile pleural effusions are generally transient and benign. The fatal ending in the lethal cases has been determined by such complications as septic endocarditis, rather than by the pleural or pulmonary disease. On the hypothesis that the eosinophilia is conditioned by the absorption of protein split products from an autolizing exudate, the mildness of eosinophile effusions is comprehensible. The finding, therefore, permits the making of a favorable prognosis.

SUMMARY.

This communication presents the account of a case of post-pneumonic pleural effusion which contained 45 per cent of eosinophiles. The report of eight similar cases gathered from the literature are summarized.

Many of the eosinophile cells of this exudate were of the mononuclear type. The patient's blood exhibited a slight eosinophilia, but did not contain any mononuclear eosinophiles. The morphology of these pleural eosinophiles suggests strongly that they have a local origin outside of the bone-marrow.

A review of the possible etiological factors in pleural eosinophilia seems favorable to the hypothesis of Schwarz:[1] that protein split products in an exudate undergoing absorption

may constitute the eosinotactic substance that produces both the general eosinophilia and the local eosinophilia.

Eosinophilic exudates have no diagnostic significance, but are of good prognostic import.

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A COLORIMETRIC METHOD FOR THE DETERMINATION OF THE HYDROGEN ION CONCENTRATION OF BIOLOGICAL FLUIDS, WITH SPECIAL REFERENCE TO THE ADJUSTMENT OF BACTERIOLOGICAL CULTURE MEDIA.

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Introduction.

The continuation within the organism of certain physiological processes depends in great measure upon the character and the constancy of the reaction of the body fluids. Changes in either will be attended by serious consequences to the cells and enzymes which find the body fluids, and more especially the blood, their natural medium. The biological importance of the constancy of the reaction of the blood has been especially emphasized by the recent studies of Henderson (1). These have shown that there exists within the organism a regulatory mechanism whereby the normal reaction of the blood is permanently maintained.

Equally important is the reaction of the medium for the successful perpetuation of life outside of the organism. This is well illustrated by the well-known and intimate association between the acidity or alkalinity of solutions containing active enzymes and the rate of their activity, and also by the influence which the reaction of a bacteriological culture medium exerts upon the biological characters and the viability of bacteria. It is not unlikely, too, that the success or failure attending the cultivation of groups of cells or tissues *in vitro* depends, in no small measure, upon the reaction of the plasma; indeed, the frequent transfer of such tissues from media containing the products of their metabolism to fresh plasma prolongs their life. The proper adjustment of the reaction of a biological fluid is, therefore, of the greatest importance for the favorable progress of many physiological processes.

As will be shown later, an exact knowledge of the reaction of a medium can be gained only from a determination of its hydrogen ion concentration. It is the purpose of this paper to present a simple colorimetric method which makes it possible to determine with considerable accuracy and rapidity the hydrogen ion concentration of biological culture fluids, and to show how such media can be adjusted to any optimal concentration of ionized hydrogen.

The Reaction of a Solution.

Recent progress in our knowledge of the physico-chemical properties of solutions has changed considerably our conception of the reaction of a solution. The importance attributed to indicators in ascertaining the reaction of a medium, and to their value in the readjustment of such a medium to the proper reaction by titration, is gradually dwindling before the extensive knowledge gained by modern physico-chemical studies. Indicators, as we now know, do not necessarily change color at the neutral point, but rather at a definite equilibrium of hydrogen and hydroxyl ions which is peculiar to each indicator, this point of change being dependent upon the chemical constitution of the indicator. It follows, therefore, that the determination of the reaction of a medium by titrating to a convenient end-point is without real significance.

According to the theory of solutions, the acidity in water is explained by the occurrence of hydrogen ions, formed from dissolved electrolytes, in excess of hydroxyl ions; neutrality is, therefore, the condition when, as in pure water, the two concentrations are equal. Because it is easier and more accurate to determine the hydrogen rather than the hydroxyl

ion concentration of a solution, it has become the established usage to express its reaction in terms of hydrogen ions.

PRESENT METHODS OF ADJUSTING THE REACTION OF CULTURE MEDIA.

In most bacteriological laboratories of this country adjustment in the reaction of culture media by titration has largely replaced all other methods. In a very recent paper Clark (2) has critically reviewed the method of "titratable acidity," and has set forth in a comprehensive way the reasons why the titrimetric method in its present form is inaccurate.

The inadequacy of the method of titration is attributable chiefly to the physico-chemical properties of the available indicators. The indicator most commonly employed for the titration of media is phenolphthalein which, like most indicators possesses no true end-point, since its zone of color change is broad, lying between the hydrogen ion concentration of $p\dot{H}=8.00$ and $p\dot{H}=10.00$.[1] If the tint of phenolphthalein at $p\dot{H}=8.50$ is taken as a standard end point it is possible to show that media corrected from this point to definite degrees on the Fuller scale have different hydrogen ion concentrations.

This discrepancy can be demonstrated quite readily, if one chooses at random various samples of laboratory media and compares the titratable acidity with the actual hydrogen ion concentration as measured colorimetrically. Table I illustrates the results of such a comparative study of twenty different batches of media. Similar observations were made by Clark who compared the titration curves obtained in the usual way with the determinations made by the use of the hydrogen electrode.

TABLE I.

A COMPARISON BETWEEN THE DEGREES IN REACTION (FULLER SCALE) AND THE HYDROGEN ION CONCENTRATION OF VARIOUS MEDIA.

No.	Medium.	Degrees in Fuller Scale.	Hydrogen Ion Concentration. Value for $p\dot{H}$.
1	Plain broth	+0.8	7.3
2	Plain broth	+0.4	7.8
3	Plain broth	+0.5	7.5
4	Plain broth	Neutral	8.4
5	Plain broth	+1.0	7.7
6	Veal-infusion	+1.0	7.1
7	Veal-infusion	+0.5	8.1
8	Veal-infusion	+0.9	7.6
9	Sugar-free broth	+0.9	7.58
10	Plain broth	+0.8	6.9
11	Liebig's broth	+0.5	7.9
12	Extract	+1.0	7.2
13	Ox-heart broth	+1.1	6.9
14	Liebig's broth	+0.8	6.9
15	Plain broth	+0.8	7.1
16	Chicken broth	+1.1	7.2
17	Glycerine broth	+1.0	7.45
18	Liebig's broth	+0.8	7.0
19	Plain broth	+1.0	6.6
20	Liebig's broth	+0.8	7.0

[1] The significance of the expression $p\dot{H}=p$ to designate the hydrogen ion concentration will be explained in a subsequent paragraph.

Unfortunately the use of the hydrogen electrode which gives the most accurate knowledge of the reaction of a medium in terms of the concentration of hydrogen ions is not suitable for practical use. Besides being time-consuming [2] the gas chain electrometric method necessitates special training in physico-chemical technique.

Heretofore the colorimetric method has not given promise, because of the lack of a suitable indicator, and because of the presence of coloring matter in the fluids to be tested. We believe, however, that both of these difficulties have been overcome in the procedure to be described.

PRINCIPLES OF THE COLORIMETRIC METHOD.

Already brief mention has been made of the principle which underlies the use of indicators in the titrimetric method. It was pointed out that the change in color of an indicator during an ordinary titration means that the hydrogen ion concentration of the solution has attained a certain degree characteristic for that indicator. Different indicators show color changes at varying degrees of hydrogen ion concentration. For example, the color of phenolphthalein changes from colorless to red between the values $p\dot{H}=8.00$ and $p\dot{H}=10.00$ (1×10^{-8} and 1×10^{-10}); whereas methyl orange passes from its full acid color over into its alkaline color as the hydrogen ion concentration falls from $p\dot{H}=3.0$ to $p\dot{H}=4.7$ (1×10^{-3} and 4×10^{-5}). At intermediate points various shades of color are obtained, a certain color indicating a definite hydrogen ion concentration.

Through the investigations of Friedenthal (3) and Salm (4) and of Sörensen (5), we now know the range of color change of a large number of indicators. From the large group studied several have been chosen for practical use, which, because of the extent of their range of color and because of the only slight interference of proteins in the test solutions, are of particular value for studies on hydrogen ion concentration.

In carrying out the colorimetric method it is necessary to have a series of standard solutions of known hydrogen ion concentration, and an indicator exhibiting a wide range of easily distinguishable color changes at hydrogen ion concentrations approximating those of the solutions to be tested. The procedure of making the readings is then quite simple, since it is necessary only to add an equal amount of indicator both to the standard solutions, and to the test solution, and to determine which of the colors in the standard series most closely matches that of the solution tested.

STANDARD SOLUTIONS AND METHOD OF NOTATION.

The standard solutions used in the method to be described were those recommended by Levy, Rowntree and Marriott (6) for the determination of the hydrogen ion concentration of the blood. These consist of standard phosphate mixtures pre-

[2] McClendon (Am. Jour. Physiol., 1915, XXXVIII, 180, 186) has described a new hydrogen electrode and a direct reading potentiometer, the use of which reduced the time necessary for a determination from forty to about two or three minutes.

pared according to the directions given by Sörensen (7). Since phenolsulphonephthalein shows definite variations in quality of color with small differences in hydrogen ion concentration between $p\dot{H}=6.4$ and $p\dot{H}=8.4$, it was chosen by these workers as the most suitable indicator. Experience in the use of these standard solutions containing phenolsulphonephthalein has further emphasized its value as an indicator for this work, not only because of the great breadth of its color range on either side of the neutral point, but also because of the ease with which the various gradations of color can be differentiated, even in the presence of the pigments which occur in most biological fluids. Furthermore, as Sörensen (8) points out, the fact that the phthalein group of indicators is more suitable for use in the presence of proteins or their split-products makes them especially valuable in studying the reaction of biological fluids by the colorimetric method.

In recording hydrogen ion concentration it is most convenient to use logarithmic notation as employed by Sörensen (9) rather than to record the actual concentrations because the significant variation is in the logarithm of the numbers which represent the quantity of hydrogen ions. For instance, N/10 hydrochloric acid is 0.091 N with respect to its hydrogen ions, and the hydrogen ion concentration is expressed conveniently as 9.1×10^{-2} or simply $10^{-1.04}$, the index, -1.04, being the logarithm of 0.091. The method of notation is still more simplified by dropping the 10 and minus sign and designating the hydrogen ion concentration by the expression $p\dot{H}=1.04$, where $p\dot{H}$ is the hydrogen ion exponent.

TABLE II.

EQUIVALENTS OF THE LOGARITHMIC VALUES $p\dot{H}=6.4$ TO $p\dot{H}=8.4$ IN ACTUAL CONCENTRATIONS OF IONIZED HYDROGEN.

Logarithm $p\dot{H}$.	Actual Hydrogen Ion Concentration $\dot{H}$.	Logarithm $p\dot{H}$.	Actual Hydrogen Ion Concentration $\dot{H}$.
6.4	4.0×10^{-7}	7.5[3]	0.32×10^{-7}
6.6	2.5×10^{-7}	7.6	0.25×10^{-7}
6.8	1.6×10^{-7}	7.7	0.2×10^{-7}
7.0	1.0×10^{-7}	7.8	0.16×10^{-7}
7.1	0.8×10^{-7}	8.0	0.1×10^{-7}
7.2	0.63×10^{-7}	8.2	0.063×10^{-7}
7.3	0.5×10^{-7}	8.4	0.04×10^{-7}
7.4	0.4×10^{-7}		

[3] The hydrogen ion concentration of the blood averages about 0.3×10^{-7} or $p\dot{H}=7.5$.

In Table II is given the equivalent of the logarithmic notation in actual concentrations of hydrogen ions. Only such equivalents are given which fall within the range of color change for phenolsulphonephthalein.

METHOD.

1. *Method Used in Comparing Colored Fluids.*—One of the greatest obstacles met with in the application of colorimetry to the determination of the ionization of biological fluids is the turbidity and the pigment present in the majority of such fluids. It is obvious that the addition of an indicator to a solution which is already colored gives rise to a tint which cannot be matched against a standard color scale made up with distilled water. This difficulty has been overcome by various workers in different ways: Sörensen (10), for instance, recommends the addition to the standard solutions of several drops of a solution of some neutral dyestuff so as to compensate for the color of the fluid under investigation. Similarly, turbid solutions can be compared by adding to the standard solutions varying amounts of a freshly prepared suspension of barium sulphate. Such procedures, as must be quite apparent, render the method more complicated and less accurate.

Realizing that this difficulty had to be overcome before the method could be made applicable, we tried various means of freeing such solutions of their color—dialysis, adsorption, and ultra-filtration. The method of dialysis, recommended by Levy, Rowntree and Marriott (11) for determining changes in the hydrogen ion concentration of the blood was first tried. This procedure, although invaluable for blood determinations, cannot be made applicable to studies on the hydrogen ion concentration of biological fluids. As we know, these fluids contain substances, chiefly the phosphates, carbonates, and colloids, which tend to preserve the original hydrogen ion concentration of the solutions. The value of these so-called "buffers" must be determined, if such fluids are to be adjusted to any desired ionization. In tests upon the dialysate, however, the influence of these "regulators" is not fully ascertained. The use of filtration through collodion membranes, although more accurate, is more difficult and equally objectionable for the reasons just given.

The removal of coloring matter by adsorbents like charcoal and Kieselguhr was early discarded, because both of these substances contain free alkali which changes the hydrogen ion concentration.

In order to obviate all of these difficulties, we have constructed a simple device[4] (Fig. 1), whereby the medium tested serves as a background for the standard test color to which it imparts its own characteristic quality of color, thus making the color of the fluid to be tested directly comparable with the standard test solutions. This apparatus[5] consists of the parts pictured (Fig. 1): A block of wood about three inches long, two inches wide and one and a half inches thick serves for the construction of the comparator. Into this block four holes, *A, B, C, D,* are bored *vertically;* these are arranged in two pairs, one beside the other. Slots *S* and *S'* are then cut through the holes. If test tubes of the proper thickness are now inserted into holes *A, B, C,* and *D,* and the apparatus is held against a white background, the light in passing through each slot must pass through the two pairs of tubes.

[4] After constructing our instrument we found that Walpole (Jour. of Biol. Chem., 1910-1911, V. 207) has made use of the same principle for reading colored fluids. Instead of having the four test tubes arranged parallel to one another, he has placed them end on in pairs.

[5] Inasmuch as the test consists merely in comparing the qualities of colors and not their intensities, as is done in ordinary colorimetry, it was thought advisable to use the term comparator rather than colorimeter for the apparatus.

The tube in *A* is the standard comparison tube of known hydrogen ion concentration. Into the hole *B* is placed the tube containing the fluid to be tested plus the correct amount of indicator. To compensate for the color of the test fluid a sample of this without indicator is placed into *C* which is just behind the standard test color. Into *D* is placed a tube containing distilled water; this tube is used merely to make the field of view of both slots of the system similar.

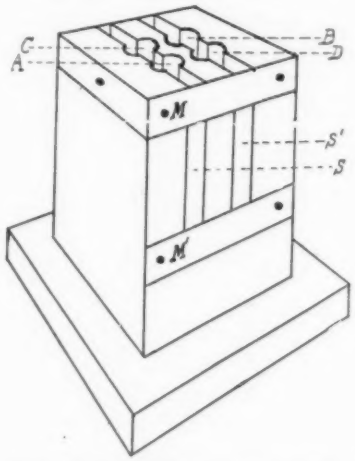

FIG. 1.—Diagram of Comparator. Into the holes *A*, *B*, *C*, *D*, are placed the four test tubes: *A* receives the standard comparison tube; *B* receives a tube containing the medium plus indicator; into *C* is placed the test solution to compensate for the natural color of the medium, and into *D* a test tube containing water. *S* and *S'* are the slots through which the colors are matched. *M* and *M'* are metal bands designed to equalize the portions of color fields exposed to view.

The titrations are most conveniently carried out in a specially constructed tube shown in Fig. 2. The acid or alkali used for

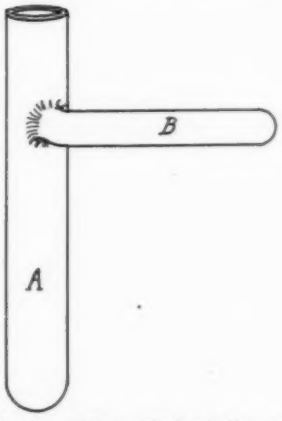

FIG. 2.—Diagram of Titration Tube. Test solution and acid or alkali are mixed in part *A*; comparisons of the color of the solution are made in part *B*, which is inserted into hole *B* of the comparator. Tube *B* is offset from part *A*, in order that part *A* will not crowd the other tubes in the comparator.

the titrations is run into the larger tube and thoroughly mixed with the test fluid. For making the comparisons, the fluid is run into the side tube, which is of the same internal diameter and thickness as tubes *A*, *C*, and *D;* this tube is inserted into the hole *B* of the comparator.

In making a reading that standard tube is chosen which at first glance appears most nearly like the color of the fluid tested. Then comparisons are made with the standard just above or below in the scale, until the closest approximation is obtained. In this way it is possible to read quite accurately between any two parts on the standard scale. It has been our experience that this method of making readings is applicable to most of the biological fluids possessing any great transparency and whose natural color is not too intense. For determinations upon yellow and straw-colored fluids it is especially useful, since phenolsulphonephthalein, in the presence of an alkali, imparts to them a brownish red tint, which can be readily matched by blending the natural color of the medium with that of the appropriate standard solution, as is done in the comparator.

2. *Preparation of the Reagents.*—In addition to the indicator N/20 acid and alkali are needed for standardization and N/1 acid and alkali for adjusting the medium to the desired concentration of ionized hydrogen.

The same strength of indicator is used in the titrations as was added originally to the standard test solutions. This is an aqueous 0.01 per cent solution of phenolsulphonephthalein made up as follows: A measured volume of indicator is obtained from a standardized solution[6] (1 cc=6 milligrams) is added to the required amount of distilled water. Of this a measured volume is taken and boiled for several minutes to expel the carbon dioxide. The solution is then made up to the original volume, so as not to alter the concentration of the indicator.

In order to keep the concentration of indicator during titration the same as its concentration in the standard comparison tubes (0.3 cc. to 3 cc. or 1 to 11), the solutions of N/20 acid and alkali used for titration are so made up that one-eleventh of their volume consists of the indicator solution. For instance, two liters of such a solution[7] are prepared according to the following formula:

Acid or alkali N/10	1000 cc.
Indicator, 0.01 per cent	182 cc.
Distilled water to make	2000 cc.

These solutions containing the indicator are used, however, only if the method is carried out according to procedure B, described below.

The normal solutions of acid or alkali are measured, sterilized and again made up to the original volume. Adjustments

[6] This is the well-known standardized solution of phenolsulphonephthalein prepared by Hynson, Westcott & Company, of Baltimore, Md., for testing kidney function.

[7] This solution must be protected from light, moisture, and carbon dioxide. If the vessel containing it is covered with a box and the glass tubing leading from it to the graduated pipette is surrounded with an opaque paper, the solution can be kept for a long time without fading of the indicator. The solution is protected from moisture and carbon dioxide by inserting into one opening of the stopper a tube containing potassium hydroxide and calcium chloride.

in the reaction of bacteriological culture media are to be made after sterilization with sterile acid or alkali for reasons which will be discussed later. For the adjustment of other culture fluids, however, no such precautions are necessary.

3. *Preliminary Test.*—The medium is tested first to ascertain what its ionization is before adjustment. This preliminary test can be carried out quickly: To 3 cc. of fluid is added 0.3 cc. of a 0.01 per cent solution of the indicator, the fluid being read directly in the comparator. In most instances the culture fluid has been roughly adjusted by the usual methods so that its reaction falls within the limits of the scale ($p\dot{H}=6.4$ to $p\dot{H}=8.4$). If the medium has not received a preliminary adjustment of reaction, it may be too acid or too alkaline to be read directly. In that event titrations are carried out in the manner to be described. From such titrations is determined the amount of acid or alkali needed to bring a liter of the medium tested from its present reaction to a desired optimal ionization.

4. *Method of Titration—Procedure A.*—It may be well, before describing the manner of carrying out the titration which was finally adopted because of its greater simplicity, to present the method as it was first tried. In procedure A the several steps in the titration, instead of being combined as in procedure B to be described below, are carried out separately.

To each of ten test tubes[a] of the same internal diameter and thickness as those containing the standard solutions are added 5 cc. of the medium tested. From a one cubic centimeter pipette graduated into hundredths is added N/20 acid or alkali, 0.1 cc. to the first tube, 0.2 cc. to the second and so on up to 1 cc. to the tenth tube. An amount of the indicator solution corresponding to one tenth of the whole volume is now added to each tube. The amounts of the acid or alkali and of the indicator solution added to each tube in this procedure are given in Table III. This gives a series of tubes containing

TABLE III.

AMOUNTS OF N/20 ACID OR ALKALI AND AMOUNTS OF INDICATOR SOLUTION REQUIRED FOR EACH OF 20 TUBES TITRATED ACCORDING TO PROCEDURE A.

No. of Tube.	1	2	3	4	5	6	7	8	9	10
N/20 acid or alkali in cc.	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Amount of indicator in cc.	0.31	0.32	0.33	0.34	0.35	0.36	0.37	0.38	0.39	0.40

No. of Tube.	11	12	13	14	15	16	17	18	19	20
N/20 acid or alkali in cc.	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0
Amount of indicator in cc.	0.41	0.42	6.43	0.44	0.45	0.46	0.47	0.48	0.49	0.50

[a] The titration of ten such tubes will ordinarily suffice if the medium has been roughly adjusted to begin with. In Table III are given the amounts of alkali and indicator to be added to 20 tubes should it be necessary to carry the titrations above the tenth tube.

the medium in a graded scale of hydrogen ion concentration and comparable in quality and intensity of color with the standard comparison tubes.

From among the ten tubes is chosen the one whose color most closely approximates that of the standard solution to which it is compared. The desired ionization may lie at a certain point between any two of the tubes of the series, in which case it is necessary to interpolate. If, for instance, tube No. 1 corresponds to the value $p\dot{H}=7.3$ and tube No. 2 to $p\dot{H}=7.6$, and the hydrogen ion concentration desired in $p\dot{H}=7.5$, the correct amount of N/1 acid or alkali to be added will lie on the curve two-thirds of the distance between that required to obtain the ionization 7.3 and that needed to give the value $p\dot{H}=7.6$.

5. *Procedure B.*—For practical use it has been found advisable to combine some of the steps in the titration so as to increase the rapidity of the method without affecting its accuracy. Instead of adding the alkali and the indicator separately to each tube, the two solutions have been combined in the manner already stated in the paragraphs on the preparation of the reagents. This solution is kept in a vessel shielded from the light and the apparatus is so arranged that the solution can be delivered directly into a graduated one-cubic-centimeter pipette, provided with a ground glass stopcock on the principle of a burette. With such an arrangement, the titration can be carried out quickly and the amounts of acid or alkali used are read directly on the pipette.

The method is further simplified because the titrations can be carried out with 3 cc. instead of 30 cc. of the medium, as in procedure *A*. Furthermore, greater accuracy is attained, since the readings in hundredths of a cubic centimeter can now be made directly on the pipette. This does away with the necessity of interpolation for amounts between tenths of a cubic centimeter—a process which is subject to inaccuracies. Readings on the pipette in terms of the N/20 solutions used for titration can be converted directly into N/1 acid or alkali per liter by reference to Chart I, which will be described below.

The method of making the comparisons is identical for both procedures, *A* and *B*.

6. *Method of Adjusting the Media.*—The manner of adjusting the medium to the desired hydrogen ion concentration may be made clear by a specific example. The medium which has been roughly standardized to +0.5 or +1.0 (Fuller scale) is sterilized in amounts, the volumes of which have been previously measured. This may be done in ordinary flasks, which have been graduated before use to a definite volume, so that any fluid lost by evaporation during sterilization may be made up by the addition of sterile distilled water. If it is desired, for example, to adjust such a medium to the hydrogen ion concentration of the blood, which corresponds to about $p\dot{H}=7.5$ on the scale, a 3 cc. sample is titrated, as already explained, until a color is obtained which matches 7.5 on the scale. Now the amount of N/20 alkali used is read directly on the graduated pipette. Should this reading be 0.46 cc., for instance, its equivalent in terms of N/1 alkali per liter would

be 9 cc. This conversion of N/20 into N/1 alkali can be made directly from Chart I, on which the N/20 solution is plotted as abscissæ and the N/1 solution as ordinates. If now 9 cc. of N/1 alkali be added to a liter of the medium, the desired hydrogen ion concentration will be obtained. Should the medium be alkaline to start with, it is, of course, necessary to titrate with N/20 acid and to adjust the medium with an equivalent amount of normal acid. For this correction the lower curve of Chart I is used.

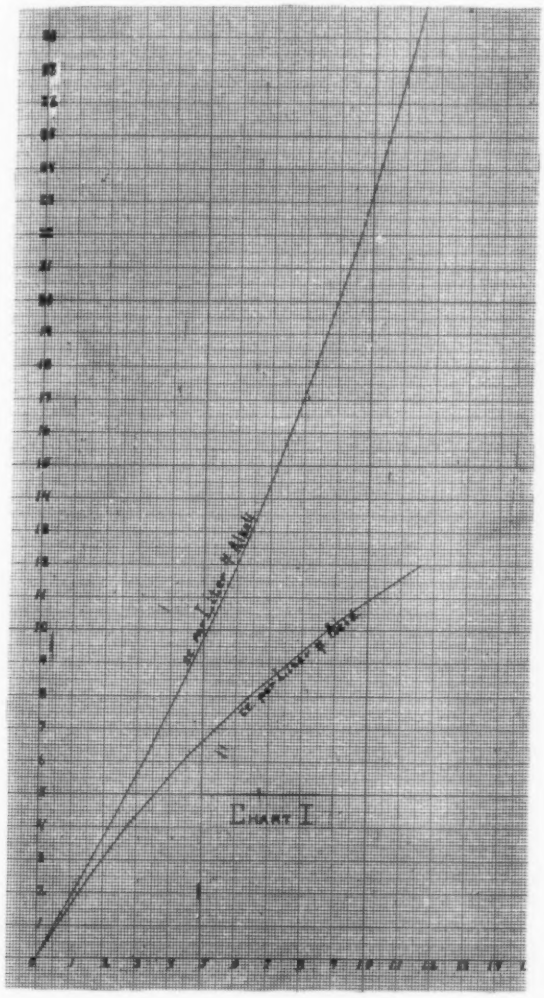

CHART I.—Curves indicating the actual amounts of N/1 acid or alkali necessary to adjust one liter of medium to the desired hydrogen ion concentration, as indicated by the amount of N/20 acid or alkali used.

Although the titrations are made with N/20 acid or alkali solutions in order to insure greater accuracy in measurement, it is desirable for practical purposes to make the adjustment with normal acid or alkali so as not to dilute the media too much. The conversion of the amounts of N/20 solution used into the corresponding amounts of N/1 solution required per liter is accomplished most readily and accurately by plotting a curve. Such a curve must take into account three factors: the alteration in volume due to the addition of concentrated rather than dilute alkali or acid; the differences in the dilution of the "buffers" of the medium, in the one instance by N/20 solution, and in the other by N/1 solution; and lastly, the degree of correspondence between the N/20 solution used for the titration and the N/1 solution used for adjusting the medium.

Only the first of these conditions can be satisfied by a curve plotted from theoretical calculations. In fact the use of such a curve has convinced us of its inaccuracy. In order to correct for all three of the variables, it was found necessary to plot a curve from data obtained by the titration of an average laboratory medium. This is done in the following manner: To five 25 cc. samples from each of two media, one originally acid and the other alkaline in reaction, was added N/1 alkali and acid in the amounts of 0.1 cc. to the first sample, 0.2 cc. to the second and so on up to the last. From each of these samples 3 cc. were then withdrawn and to each was added 0.3 cc. of the indicator. A 3 cc. sample of the same medium was now titrated with N/20 alkali or acid, after the addition of 0.3 cc. of the indicator solution, until its color matched successively the color of each of the five tubes. The amounts of N/20 solution required were plotted as abscissæ and the corresponding amounts of N/1 solution as ordinates.

The upper and lower curves of Chart I express the relation existing between the number of cubic centimeters of N/1 alkali or acid per liter of medium and the number of cubic centimeters of N/20 alkali or acid per 3 cc. of medium necessary to bring about the same hydrogen ion concentration. In this way account is taken also of the effect upon ionization of the "buffers," by the dilution of the medium in the one instance by N/20 solution and in the other by N/1 solution. Such curves plotted for an average medium* will be found true for almost all similar media.

It is recommended that each worker using this procedure plot such reference curves. This will add greatly to the accuracy of the method, since, besides correcting for volume and dilution of "buffers," these curves correct also for any error which may arise from lack of correspondence between the N/20 solutions used for titration and the N/1 solutions used for adjusting the media.

In order that the application of this method may yield satisfactory results in the adjustment of bacteriological culture media, it is essential, in the first place, that the medium be roughly adjusted in the beginning, and secondly, that the correction in reaction be made with a sterile acid or alkali. Such a rough correction conducted in the usual manner serves a two-fold purpose: (1) it brings the reaction within the range of the standard scale, thus making a direct reading in terms of hydrogen ion concentration possible; and (2) it necessitates the addition of smaller quantities of acid or alkali for the

*Most of the media tested in this laboratory were prepared by extracting meat for 18-24 hours in the cold and then adding to this extract one per cent peptone, either Witte or Chapoteaut.

final adjustment of the sterile medium. This obviates the dilution of the active ingredients and the possibility of precipitate formation, which may result from the addition of too large quantities of acid or alkali.[10]

The fallacy of correcting by the titrimetric method the reaction of a medium before sterilization applies all the more to the procedure under consideration. It is now well known that media show not only an increase in titratable acidity after sterilization (12), but, as would be anticipated, sterilization changes the equilibrium of hydrogen and hydroxyl ions (13). This change may or may not be accompanied by precipitation. It follows, that adjustments in the hydrogen ion concentration made before sterilization do not hold for media after they have been sterilized. This is all the more true of the finer adjustments in the ionization which are obtainable by the procedure outlined. It has, therefore, become the custom of some workers (14) to correct their media by adding a sterile acid or alkali to the sterilized medium.

The matter is much simplified, however, where the question of sterilization does not enter, as in the case of other culture fluids, for instance, those containing active enzymes. The latter can be readily adjusted to any optimal ionization directly, if their range of activity lies within the concentration of hydrogen ions represented by the standard solutions used.

Results of the Method.

In order to determine the accuracy and the usefulness of the method, titrations were carried out on various samples of media—bouillon, agar, and gelatin, chosen at random from the different batches in the laboratory. Most of these had been adjusted previously according to the Fuller scale, so that their reaction fell within the limits of the colorimetric scale. In practice such media are usually found acid, necessitating, therefore, an addition of alkali to adjust them to the desired reaction. In order to test out the applicability of the method to the adjustment of media found to be too alkaline, titrations were also carried out with N/20 acid instead of alkali upon samples which had been previously made alkaline.

After determining the amount of N/1 alkali or acid needed to bring the test medium to the desired hydrogen ion concentration, this amount was added to a 25 cc. sample and a determination again made of the adjusted medium.

Forty-nine determinations were made upon twenty-three different samples of media. The results of the titrations are recorded in Tables IV and V. In Table IV are listed the various media just as they were prepared for use in the laboratory, while in Table V are recorded the results of titrations of media made alkaline for experimental purposes.

It will be seen that, for the most part, the correspondence between the hydrogen ion concentration desired and that obtained by the addition of the correct amount of alkali or acid is very close. Such accuracy in titration is readily obtained after sufficient familiarity with the technique and the standard color scale.

In several instances determinations of the hydrogen ion concentration of solid media were made. Media containing agar or gelatin were first rendered fluid by bringing them to the proper temperature. To the fluid solution was then added the indicator. The medium was inverted in the test tube several times to distribute the color evenly, and allowed to solidify.[11] Determinations of the hydrogen ion concentration of the solidified medium could then be made directly in the comparator. Most of the samples tested in this manner were sufficiently transparent to make a color comparison extremely accurate. In a few cases samples of agar were adjusted with the calculated amount of acid or alkali and determinations of the adjusted samples of the solidified media were made, as in the case of fluid media. These tests convinced us of the usefulness of the method for the determination of the hydrogen ion concentration of solid media.

Usefulness and Applicability of the Method.

In discussing the practice of adjusting media by the method of titration in general use, attention was called to the variations in hydrogen ion concentration possessed by media adjusted to the same point on the Fuller scale. In spite of these variations in reaction, however, most bacteria have been successfully cultivated. Clark's experience has been that *B. coli* and certain streptococci will grow in media with hydrogen ion concentration values varying from $pH = 5.5$ to $pH = 9.0$. This fact is now readily explained by the presence in such media of "regulators" or "buffers." These, as already explained, prevent rapid changes in hydrogen ion concentration, which may be produced by the metabolic products of bacterial growth. This explains the value of an infusion rich in "buffers" (principally the phosphates, carbonates, and amphoteric proteins) whose ionization is little altered by a considerable variation in titratable acidity.

Chart II illustrates graphically the difference in the "buffer effect" of several such media, as measured by the amount of N/20 acid or alkali needed to bring each from one concentration to another given concentration of hydrogen ions. It will be observed that the media rich in "buffers" show flatter curves than those that are poor in "buffers," for the reason that a transition from one point on the scale to another requires more acid or alkali. Similar curves obtained by the use of the hydrogen electrode have been plotted by Clark (15). It is more simple, however, to obtain such curves by using the colorimetric method. Their value rests in the important information they give concerning the "buffer" content of a medium upon which depends, in large measure, its usefulness for the growth of bacteria.

[10] As Clark (p. 127) points out, proteins exist in solution only within certain narrow limits of hydrogen ion concentration, and the precipitation of these and other substances of a complex medium occurs as the hydrogen ion concentration is changed.

[11] Readings should be made on the solidified medium at a constant room temperature, since the hydrogen ion concentration changes with the temperature.

TABLE IV.

TITRATION OF ACID MEDIA SHOWING VALUE OF pH DESIRED AND THAT OBTAINED BY ADDING CORRECT VOLUME OF N/1 ALKALI TO A 25 CC. SAMPLE OF MEDIUM.

No. of Exp.	Date.	Media.	Titration by Fuller Scale.*	Preliminary test.	Standard desired.	N/20 alkali in cc.	N/1 alkali added per 25 cc.	Value of pH obtained.	Remarks.
1	Aug. 6	Veal-infusion.	+1.0	Below 6.4	7.5	0.46	0.225	7.45	
2	Aug. 7	Plain broth.	+0.8	6.9	7.6	0.17	0.073	7.55	
3	Aug. 12	Liebig's broth.	+0.8	6.9	7.6	0.195	0.087	7.55	Medium poor in "buffers" as shown by titration curve.
					7.7	0.20	0.095	7.7	
4	Aug. 16	Plain broth.	+0.8	7.15	7.6	0.13	0.06	7.6	
					7.9	0.195	0.088	7.9	
					8.2	0.285	0.13	8.15	
5	— —	Extract.	+1.0	6.9	7.5	0.08	0.04	7.55	Plotted as Curve V, Chart II; medium poor in "buffers."
					7.9	0.21	0.096	7.9	
6	Aug. 11	Ox-heart broth.	+1.1	6.9	7.4	0.25	0.114	7.4	Plotted as Curve VII, Chart II.
					7.6	0.30	0.14	7.55	
					7.8	0.35	0.164	7.75	
7	Aug. 11	Ox-heart broth —no peptone.	— —	Below 6.4	7.2	0.36	0.17	7.15	Plotted as Curve VI, Chart II.
					7.3	0.43	0.21	7.3	
8	Aug. 16	Chicken broth.	+1.1	7.25	7.6	0.48	0.23	7.65	
9	Aug. 17	Plain agar.	+1.0	7.1	7.9	0.26	0.12	7.9	
10	Aug. 17	Sugar-free broth.	— —	7.2	7.4	0.185	0.085	7.45	
					7.6	0.26	0.12	7.55	
11	Aug. 17	Plain broth.	+1.0	6.9	7.3	0.195	0.09	7.3	
					7.7	0.275	0.13	7.65	
					7.9	0.375	0.18	7.9	
12	Aug. 17	Glycerine broth.	— —	7.45	7.7	0.08	0.04	7.7	
					7.9	0.15	0.07	7.9	
13	Aug. 26	Liebig's broth.	+0.9	Below 6.4	7.0	0.285	0.13	7.05	
					7.4	0.35	0.17	7.35	
				Below	7.7	0.435	0.21	7.7	
			+1.0	6.4	7.5	0.37	0.19	7.5	
14	Aug. 30	Ox-heart broth.	— —	6.9	7.3	0.17	0.08	7.25	
			— —	7.0	7.8	0.285	0.13	7.8	
15	Aug. 30	Ox-heart broth plus 10% bile.	+1.0	6.9	7.6	0.30	0.15	7.55	
					7.4	0.25	0.12	7.35	
			— —	7.1	7.7	0.21	0.1	7.65	

* Recorded readings by Fuller method were made before sterilization.

TABLE V.

TITRATION OF ALKALINE MEDIA SHOWING VALUE OF pH DESIRED AND THAT OBTAINED BY ADDING THE CORRECT VOLUME OF N/1 ACID TO A 25 CC. SAMPLE OF MEDIUM.

No. of Exp.	Date.	Medium.	Titration by Fuller Scale.	Preliminary Test.	Standard desired.	N/20 acid in cc.	N/1 acid added per 25 cc.	Value of pH obtained.	Remarks.
1	Aug. 18	Plain broth.	—	8.3	7.9	0.33	0.12	7.9	Plotted as Curve I, on Chart II.
					7.4	0.49	0.16	7.45	
2	Aug. 19	Sugar-free broth.	—	8.3	7.8	0.21	0.08	7.85	Plotted as Curve II, on Chart II.
					7.4	0.33	0.115	7.45	
					7.3	0.44	0.15	7.3	
3	Aug. 20	Liebig's broth.	—	7.7	7.2	0.10	0.04	7.2	Plotted as Curve III, Chart II.
4	Aug. 20	Liebig's broth —no peptone.	—	8.4	7.9	0.44	0.15	7.9	
					7.6	0.64	0.20	7.6	
					7.3	0.82	0.24	7.3	
5	Aug. 21	Ox-heart broth —no peptone.	—	—	7.5	0.33	0.12	7.5	Plotted as Curve V, Chart II.
					7.1	0.52	0.17	7.1	
6	Aug. 24	Ox-heart glucose broth.	—	7.6	7.1	0.10	0.04	7.1	
7	Aug. 26	Liebig's broth.	—	8.35	7.9	0.21	0.08	7.9	
					7.5	0.44	0.15	7.55	
					7.2	0.56	0.18	7.25	
8	Aug. 30	Ox-heart broth plus 10% bile.	—	8.3	7.9	0.33	0.12	7.85	
					7.3	0.56	0.18	7.3	

The real usefulness of the colorimetric method, however, must be sought in its greater accuracy and in its wide scope of applicability. It will be found of great value in the adjustment of the hydrogen ion concentration of media for organisms

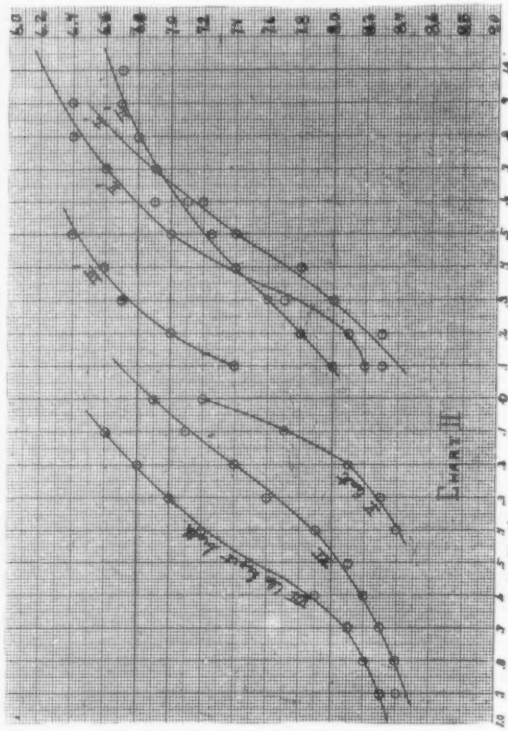

CHART II.—Titration curves of various media obtained with phenolsulphonephthalein, showing the effect of "buffers" upon hydrogen ion concentration.

which are more sensitive to the reaction of their culture fluids. The method is comparable in a way to the fine adjustment of a microscope, the method of titratable acidity serving only to adjust media coarsely for the growth of the average organism. Its further usefulness will be found in careful studies upon the morphology, mutations and metabolisms of organisms, bacteria[12] and also protozoa. Whether the colorimetric method in its present form is suitable as a substitute for those now in general use in bacteriological laboratories can be decided only after it has been accorded a more extensive application.

Already we have found the method, with some modifications, useful in determining the reaction of other biological fluids. Further studies in this direction are now being carried out in this laboratory.

In conclusion, we wish to express our indebtedness to Drs. Rowntree and Marriott for providing us with a set of the standard test solutions, made under their supervision by Mr. Dunning, of Hynson, Westcott & Company, Baltimore, Md., and for valuable suggestions regarding their use.

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[12] Blumenthal (Ztschr. f. klin., Med., 1895, XXVIII, 223) has shown that the reaction of the medium influences appreciably the relative proportions of the end-products of fermentation and putrefaction.

HODGKIN'S DISEASE OF THE INTESTINES.

WITH REPORT OF A CASE.

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It has not been a great while since the conception of Hodgkin's disease as an affection beginning always in the glands of the neck, or at least in a superficial gland group, has been questioned.

Yates[1] defines Hodgkin's disease as "an infectious noncontagious affection due to *B. hodgkinii*. It is characterized by a somewhat variable, though definite, reaction in the lymphatic and perilymphatic structures, specific changes in the blood picture, and by the manifestation of little or no tendency to spontaneous recovery." That there is a primary mediastinal type of this disease is now recognized. The tumor formations confined to the intestines, however, are very uncommon, and a case which has come under our notice seems worthy of record in the literature of this disease.

Bunting,[2] in 1910, reported his observations upon the increase of blood platelets and megalokaryocytes in Hodgkin's disease. Not only were the platelets markedly increased in number, but large forms were numerous, and many of these masses revealed pseudopod-like processes.

In 1911,[3] he reported upon a characteristic blood picture in the disease. This consists principally in an increase of the large endothelial-like cells, so-called transitional, together

with the previously noted increase in number and size of the platelets. In the four years since this publication, there has been abundant opportunity to confirm his original observations and to extend them so that one is able, from the blood picture, to tell whether a patient is improving or retrogressing.

Steiger,[4] in a long and rather elaborate discussion of Hodgkin's disease, comes to the conclusion that the blood picture is characterized by a leucocytosis of the polymorphonuclear type. He makes no mention of platelets. It is possible (although it is not so stated) that he used Ehrlich's stain. Under such circumstances, he would have failed to see the platelets. His blood picture tallies with that found by Bunting in the final stages of the disease, when the platelets actually are diminished.

Bunting and Yates,[5] in 1913, reported the discovery of a diphtheroid bacillus, showing marked pleomorphic characters, in three cases of Hodgkin's disease. Later they reported that they had reproduced the disease in a monkey. The characteristic blood picture was present.

In a later communication, [6 7] they report experiments which seem to leave no doubt of the transmission of the disease from one monkey to another. These cultural results have been confirmed by Rosenow,[8] Steele,[9] Verploegh,[10] Kehrer, Von Hoogenhugze, and others. The evidence now at hand seems to justify the definition of Yates given above. Clinically, we have had an opportunity of observing cases beginning in the mediastinum, as well as in other groups of glands besides the cervical.

The case here reported is the only one of its kind which has come under our notice, and one of the very few in the literature.

D. S., a Bulgarian, single, aged 27, common laborer by occupation, was admitted to the Milwaukee County Hospital, April 9, 1914, complaining that he was "sick in his stomach." He had never been ill, smoked moderately, and denied venereal disease. For about eight months he had had intermittent pain in the stomach after eating, which was not severe enough, at first, to force him to stop work. The pain, however, had gradually increased, he had vomited occasionally after meals, had become weak, and lost strength and weight so that he had been obliged to stop work in January. Since the onset of his trouble, he had had almost constant diarrhea. There had also been an intermittent cough.

He was only fairly well nourished. There were a few mucous rales at the lung apices, and slight impairment of the percussion note at both bases.

The abdomen showed a "curious distension below the umbilicus, as with gas, with apparent constriction just below the costal margin." There was no increase in liver dullness. There were no masses palpable. He was in the hospital only a few days. The most probable diagnosis seemed to be pulmonary tuberculosis, with a dry peritoneal tuberculosis.

He was readmitted May 2, 1914, having grown much weaker and more emaciated. The pain in the stomach was worse, the vomiting after meals more frequent. He was not coughing or expectorating. There was flatness over both bases of the lungs. The liver did not reach the costal margin. The appearance of the abdomen was similar to that observed on the previous admission. There were no enlarged glands anywhere.

Some fluid was removed from the right pleural cavity. The leucocytes were 7000. Differential count (Hastings' stain) showed polymorphonuclears, 60%; mat. and immat. lymp., 34%; trans. (end.) 6%; bas., 1%. The records made no mention of platelets. There was no occult blood in the stools. Several examinations for tubercle bacilli in the sputum were negative. The urine was normal. On the 13th, the leucocytes were 16,200. The patient gradually grew weaker, and died rather suddenly, with obscure abdominal symptoms, subnormal temperature and only slightly increased pulse rate, on May 23d.

Autopsy (Dr. Kristjanson), 26 hours after death.

Anatomical Diagnosis.—Acute general peritonitis, with perforation of jejunum; diffuse and nodular thickening of intestines; enlargement of mesenteric glands; acute splenic tumor; slight pleural effusion (right side); edema of lungs.

General Appearance.—The body is that of a rather poorly nourished and emaciated young white male, 150 cm. in length. There is marked post-mortem discoloration of the skin over the back of the neck and upper portion of the chest, down to the third rib. There is a slight greenish tinge to the skin over the lower half of the abdomen. The pupils are unequal; the left measures 4 mm., the right, 5 mm. in diameter. Rigor mortis is very slight in the extremities.

Abdomen.—There is some distension of the abdomen, with a tympanitic note over the central portion, but dullness in both flanks. The abdominal cavity contains about three liters of a foul-smelling, brownish semi-fluid material. The small intestines are distended and discolored and in several places are glued together by an acute fibrinous exudate. There are many nodular enlargements in the wall of the intestines. The mesenteric glands are much enlarged. The diaphragm stands at the fifth rib on the right side, at the fourth interspace on the left. The liver projects about 4 cm. below the costal border. The stomach is somewhat distended, and the anterior wall and adjacent parietal peritoneum are covered with fibrin. There are a few chronic adhesions about the spleen.

Thoracic Cavity.—The lungs nearly fill the respective pleural cavities and they meet in the median line. On the right side are a few chronic fibrous adhesions about the junction of the lobes, uniting them to the chest wall. The left lung is free; there are no adhesions about the apices. There is a small amount of bloody fluid in the right pleural cavity. A few small palpable glands are found in the anterior mediastinal space. The myocardium is brownish-red in color and fairly firm.

Lungs.—The right lung is rather voluminous; it weighs 470 grams. There are a few adhesions between the lobes. In the upper portion of the lower lobe is a small nodule, hard and firm, measuring 5 cm. in diameter, composed of encapsulated calcareous material. The dependent part of this lung is a little firmer than normal, and on section there is an excess of blood and serum. The left lung is a trifle smaller than the right. It weighs 420 grams, and is similar in appearance to the right lung. The dependent portion contains bloody fluid.

Spleen.—The spleen is quite large; it weighs 280 grams. It is bound by firm adhesions to the diaphragm. There are also adhesions about the pedicle uniting it to the transverse colon. The external surface is smooth and pale blue in color, except where it is spotted with grayish-white areas of fibrous thickening of the capsule. The cut surface shows the trabeculæ radiating from the capsule through the soft, friable, congested pulp, in which the lymph-nodes are no longer visible.

Liver.—The liver is somewhat enlarged (1600 grams). It is firm, and of a deep reddish-brown color. On section blood drips from it freely, and it presents a peculiar mottled appearance. The lobulation is indistinct. The gall-bladder is partially filled with a viscid dark-brown fluid.

Pancreas.—The pancreas shows no change on gross appearance.

Stomach.—The stomach is normal in appearance.

Intestines.—The small and large intestines and mesentery were removed in one piece. The mesentery is a mass of soft lymph-

glands that vary in size from 1 to 4 cm. in diameter. On section they seem to be confined within a definite capsule; the cut surface shows a fairly uniform whitish-gray tissue, from which a small amount of grayish material can be scraped. None of these glands show any evidence of suppuration or caseation.

Approximately 46 cm. from the pyloric end of the stomach, in the course of the jejunum, is a small opening, about 4 mm. in diameter in the serous coat of the bowel, directly opposite to the mesenteric attachment. When the intestine is opened at this point, there is found a small ulcerating area, through the base of which is a small perforation, corresponding to the opening in the external surface of the bowels. This ulcer is 9 mm. in diameter, with fairly smooth edges; the base around the perforation is bathed in a grayish necrotic material.

Throughout the entire extent of the wall of the small intestine are small and large nodular bodies. There is also a uniform thickening of the intestinal coats. About the junction of the jejunum and the ileum are several small loops of intestine, united by chronic fibrous adhesions. In the proximal portion of the mass thus formed are nodular bodies in the wall of the intestine. These, apparently, are small glands, having on section the gross characteristics noted in the mesenteric glands. These nodular masses and the thickening of the wall become more marked as one approaches the lower end of the ileum and cecum.

In the upper third of the ileum, there is a great enlargement of the intestine, which measures 7 cm. in diameter; and when a longitudinal incision of 7 cm., the length of the tumor mass, is made, the intestinal wall is found to be thickened, and measures 2 cm. On examining the interior of the bowel at this point, one finds that the transverse folds are for the most part obliterated, and there are irregular soft masses protruding into the lumen of the gut. Between this point and the cecum are encountered numerous nodular enlargements, with thickening of the intestinal walls; but these are not so pronounced as the ones just described.

About 3 ft. from the cecum, along the mesenteric attachment of the small intestines, is a tumor mass, 5 x 3 x 2.5 cm. It is covered by the serous coat, and the cut section has a grayish-white granular appearance.

The distal end of the ileum, the cecum, and a tumor mass in the mesentery are united by adhesions, forming a large nodular mass. The appendix lies curled up in a fold of this big mass. It, however, does not seem to be involved in the growth. The wall of the cecum is very much thickened, making up the major portion of the tumor. There are a few small palpable glands along the mesenteric attachment of the ascending colon. There seems to be a uniform thickening of the wall of the large bowel, yet no nodular bodies are found in the submucosa. The solitary follicles and Peyer's patches are, in places, enormously thickened, raised, and of a dull gray color.

The *right kidney* is normal in size and shape. The capsule strips off readily, leaving a smooth, but slightly mottled surface. On section, the cut surface presents a fairly normal appearance. The cortex is 4.5 mm. in thickness, and shows numerous reddish streaks, extending from the capsule towards the papillæ. The Malpighian corpuscles are not discernible in the cut section. The *left kidney* presents no essential difference. Blood drips from the cut surface of both kidneys. The *suprarenals* are very small, and on gross appearance present no visible pathological changes.

Bladder and Prostate.—The bladder is not thickened and shows no abnormal condition. The prostate is not enlarged.

Glands.—The cervical, axillary, mediastinal and femoral glands are not palpable.

Microscopical Examination.—Sections of the *lungs* show only edema. Large multinucleated cells are seen in the capillaries. These do not seem to be increased in number.

Liver.—There is general infiltration, with small and large round cells, the former having the usual structure and size of lymphocytes, the latter showing some variation in size, always being considerably larger than the former, with fairly deeply staining nucleus and a considerable amount of protoplasm. The intercolumnar liver spaces are separated by the extensive infiltration. Scattered throughout in the portal spaces are collections of lymphoid cells which form minute nodules. The cells in these nodules are of various kinds, and now and again one finds a giant cell of the Reed type, with vesicular nuclei, and of another type with small, deeply staining nuclei.

Spleen.—There is marked congestion of the organ throughout. The pulp contains little that resembles normal spleen. There is a great variety of cells, mostly round, with great numbers of plasma cells. The Malpighian bodies show profound changes. There are hyaline arteries indicating where the vessels have been; or at times there are ill-defined collections of round cells—spaced apart—with an arteriole, the wall of which has undergone hyaline degeneration. The splenic sinuses are large and crowded with blood cells. Many giant cells, containing from 5 to 10 vesicular nuclei, are found scattered through the pulp. There is a great increase in new connective-tissue fibrils, and many fibroblasts.

Intestines.—Sections taken from various portions show varying degrees of the same general picture. The epithelium is not disturbed; the basement membrane is present. The great increase in thickness of the gut is found to be due to the enormous hyperplasia of the submucous coat and dense infiltration of both muscular coats to the serosa. The individual muscle fibers are widely separated by masses of cells streaming in from the submucosa. These are mostly typical lymphoid cells, and the first impression is that the growth is a lymphosarcoma. Close study shows that there is proliferation of the reticulum; there are places where endothelioid cells are fairly numerous, and giant cells are scattered throughout. The eosinophiles are few in number. The picture is that of Hodgkin's disease.

Sections from the intestines were stained by Gram's method and careful search was made for Gram-positive bacilli. Some structures were found which were believed to be bacilli.

Some of the affected tissue was placed in antiformin, according to the method of Fraenkel and Much. We confess an inability to state that the particles taking the stain on the slide were or were not fragments of bacilli. We feel that, in the absence of a differential stain, no one can say positively that fragments on a slide after antiformin treatment of the tissue are granular forms of bacilli.

Cultures were not made, as we felt it would be useless to attempt to grow specific organisms in the face of the intense colon infection of the peritoneal cavity.

Wells and Mayer,[1] in 1904, reporting a case of "pseudoleukemia gastrointestinalis," were able to find only six cases in the literature showing extensive changes in the lymph tissue chiefly or solely of the gastrointestinal tract. In their case the chief hyperplasia was in the stomach, the walls of which were enormously thickened, the organ weighing 1350 grams. The cecum also was thickened, and resembled the stomach, "the greatest thickening being at the beginning of the appendix, where there is a mass 4 cm. in diameter." The solitary follicles and Peyer's patches were thickened. The appendix was firm, long and thick. There was a general slight, but definite, enlargement of all the superficial glands. The abdominal glands, especially the peripancreatic, were much enlarged, soft and pale. From the description of the microscopic appearances of the various gland groups, one has no doubt that to-day this case would unhesitatingly be called an instance of Hodgkin's disease, as it conforms to the criteria

FIG. 1.—Hodgkin's disease of the intestines, showing diffuse and localized infiltration of the intestinal wall and mesentery.

FIG. 2.—This section shows marked infiltration of the submucous and muscular layers of the wall of the intestine. (Leitz obj. 3; ocular No. 10.)

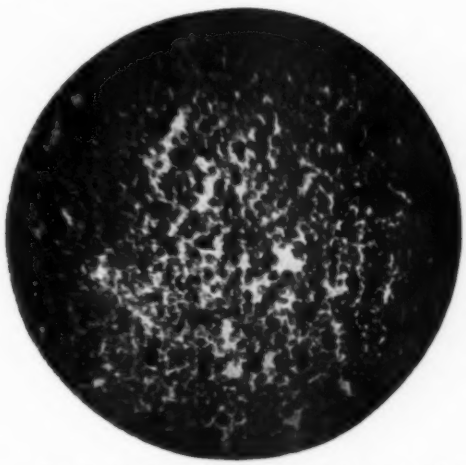

FIG. 3.—In this section are noted many endotheliocytes and endothelial giant cells in the submucosa. (B. L. obj. 4 mm.; ocular No. 10.)

FIG. 4.—This section, through a tumor mass, shows many large cells, similar to those in figure 3. (B. L. obj. 4 mm.; ocular No. 10.)

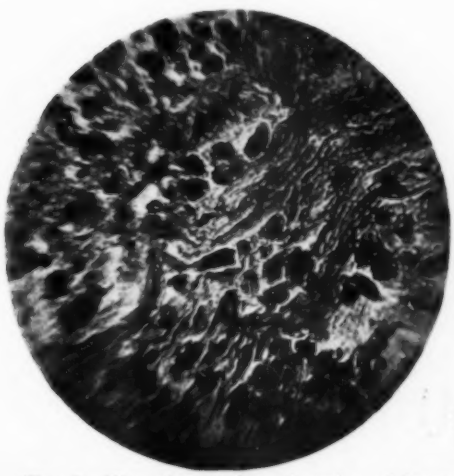

FIG. 5.—There is noted an invasion of large cells between the muscular fibers. (B. L. oil immersion 1.9 mm.; ocular No. 10.)

given by Reed, Longcope, Bunting, and others. Wells and Mayer, in their general summary, speak of their case as an instance of Hodgkin's disease.

Under the title, "Ueber einen Fall von lokalisierten Hodgkinschen Granulom der Ileozaekalklappe," Catsaras and Georgantas [12] report the case of a man 34 years old who had complained for a year of pains in the abdomen, a feeling of oppression and obstinate constipation, alternating with attacks of diarrhea. Palpation in the right iliac fossa revealed resistance and pain on pressure. The examination was, in other respects, negative.

At operation, the cecum, a large part of the large intestine, and a small part of the small intestine, were removed. The patient lived four months. He died with symptoms of dysentery and cachexia.

Examination of the tumor showed that it was submucous, the size of a mandarin orange, situated at the ileo-cecal opening. There was no ulceration; the cut section showed a homogeneous grayish-white color. The neighboring lymph-glands were slightly swollen and hard.

The histological picture was typical of Hodgkin's disease. The sections of the lymph-glands revealed similar pictures. These writers describe two kinds of giant cells: one a large cell with many vesicular nuclei; the other, a cell with dark-staining nuclei and deeply staining basophilic protoplasm. They think these latter arise from large lymphocytes. They also noted two kinds of eosinophile cells, polymorphonuclear and mononuclear. The former were found in the capillaries, the latter away from the blood channels in the tissue. They thought that the latter were lymphocytes, which had taken up the free granules of degenerated eosinophile cells.

Bunting and Yates [5] mention briefly the fact that in the intestines of a girl of 6 years, who died in a severe vomiting attack, the Peyer's patches of the intestines and the mesenteric lymph-nodes showed the changes of early Hodgkin's disease, which from clinical and post-mortem evidence must have been primarily intestinal in origin.

The portal of entry of the infection in our case must have been the intestine. This is most unusual. The histopathology, together with the Gram-positive bacteria in the affected tissue, seems to us conclusive evidence of Hodgkin's disease. Whether these cases are as rare as they seem to be is unanswerable at the present time. Possibly such cases have been diagnosed heretofore as lymphosarcoma or pseudoleukemia. The present intensive study of the disease due to *B. hodgkinii* will no doubt direct attention to cases similar to this one, and assist in furthering our knowledge of this most important group.

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Dr. Karl Van Norman has accepted a commission as Captain in the Canadian Division of the Royal Army Medical Corps, and has reported in London for service.

Dr. Carl W. Waldron has joined the British Royal Army Medical Corps.

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